ANNALS OF
INTERNAL MEDICINE

VOLUME 54 APRIL, 1961 NUMBER 4

ACUTE GLOMERULONEPHRITIS IN ELDERLY PATIENTS: REPORT OF SEVEN CASES OVER SIXTY YEARS OF AGE * †

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ACUTE glomerulonephritis is commonly regarded as a disease of childhood, adolescence, and early adulthood.[1-3] However, a large number of older patients with acute glomerulonephritis have been seen in the Cardiorenal Clinic of Peter Bent Brigham Hospital and on the wards of the Massachusetts General Hospital. The incidence of acute glomerulonephritis in elderly patients is reportedly quite rare, and only occasional references are made in the literature to its occurrence in such patients.[3, 4] This paper reports seven cases of acute glomerulonephritis in patients 60 years of age or older, and shows that acute glomerulonephritis is not restricted to children or young adults but may occur not infrequently in elderly patients.

CASE REPORTS

Case 1. An 81-year-old white man was admitted to Peter Bent Brigham Hospital because of anuria. A left nephrectomy had been performed eight years prior to admission for chronic pyelonephritis. The patient was a known diabetic requiring small daily doses of chlorpropamide. Apparently he had been in good health until

* Received for publication July 15, 1960.
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† Supported in part by the U. S. Army Medical Research and Development Command, Department of the Army, under Contract No. DA-49-007-MD-429, and in part by the National Heart Institute, National Institutes of Health, United States Public Health Service (H-444 CIO).
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about two weeks prior to admission, when in the absence of any preceding oliguria or other symptoms he became severely oliguric. Cystoscopy and retrograde pyelography performed on admission to Massachusetts General Hospital failed to reveal any abnormalities of the lower urinary tract and only 20 ml. of urine were found in the bladder. Urinalysis showed 4-plus proteinuria, and the sediment contained many red blood cells, white blood cells, and granular casts. No red blood cell casts were noted. The sputum culture revealed a moderate growth of beta hemolytic streptococcus. Subsequently, the urinary output increased gradually to a volume of 300 ml./24 hrs. Because of worsening symptoms of uremia the patient was transferred to Peter Bent Brigham Hospital for hemodialysis. On admission the patient appeared chronically ill and was extremely obtunded. Blood pressure, 140/75 mm. Hg; lungs, clear except for a few basilar râles; heart, not enlarged. There was moderate edema of pretibial and presacral regions. Serum electrolytes were as follows: sodium, 125 mEq./L.; potassium, 6.7 mEq./L.; chloride, 93 mEq./L.; fasting blood sugar, 169 mg./100 ml.; total CO_2 content, 11 mM./L.; and blood urea nitrogen 132 mg./100 ml. Urinary output ranged between 200 and 400 ml./24 hrs. Two hemodialyses were performed on the fourth and the sixth hospital days without significant clinical improvement. On the following day surgical exploration and biopsy of the right kidney were carried out. Operative findings were consistent with those of acute glomerulonephritis. The diagnosis was subsequently confirmed by microscopic examination of the kidney biopsy specimen. On the second postoperative day his blood pressure suddenly became unobtainable and the patient died. Post-mortem examination of the kidney confirmed the diagnosis of acute glomerulonephritis. However, the immediate cause of death was not established.

Case 2. A 79-year-old white man had been in excellent health until six days prior to admission, when he experienced two episodes of painless hematuria. Cystoscopy, performed at another hospital, showed extrusion of blood from both ureteral orifices. Shortly afterwards, the patient became severely oliguric and was tranferred to Peter Bent Brigham Hospital. His past history was noncontributory except for a prostatectomy 14 months prior to the present illness. Blood pressure was 170/100 mm. Hg. The chest was emphysematous, and many moist inspiratory râles were heard at both lung bases. The murmur of aortic stenosis was audible. The urine appeared grossly bloody and urinary sediments contained many white blood cells, red blood cells, and 2-plus proteinuria. No cellular casts were noted. Hematocrit was 26%. Serum electrolytes were essentially normal. Serum uric acid was 18.6 mg./100 ml., and blood urea nitrogen was 181 mg./100 ml. During the first six days urine flow was in the range of 200 ml. and gradually increased to about 2,000 ml./24 hrs. Despite diuresis the patient became more drowsy and was dialyzed, with poor clinical response. On the twelfth hospital day, he became hypotensive and died suddenly. Gross and microscopic anatomical examination of the kidneys showed acute glomerulonephritis. Other significant findings were severe bronchopneumonia and generalized arteriosclerosis.

Case 3. A 72-year-old man was admitted to Peter Bent Brigham Hospital from a nursing home, with a suspected diagnosis of pneumonia. The patient was known to have arteriosclerotic heart disease with angina pectoris and recurrent bouts of pneumonia. Three days prior to admission he became disoriented and anorectic, and developed a productive cough. On admission his blood pressure was 160/80 mm. Hg, and he appeared markedly dehydrated. The heart was not enlarged, and only a few dry basilar râles were heard in the lungs. Urine showed 3-plus proteinuria and the sediment was loaded with red blood cells and white blood cells, but no cellular casts were seen. Blood urea nitrogen was 21 mg./100 ml. Films of kidneys, ureters, and bladder showed a small right kidney with overlying calcification. The throat culture was negative for beta hemolytic streptococcus. The diagnosis of dehydration and

prerenal azotemia was considered. Despite adequate parenteral fluid therapy the patient remained oliguric throughout his hospital stay, with progressive rise in blood urea nitrogen. On the eleventh hospital day the patient died suddenly. Post-mortem findings revealed acute glomerulonephritis. Other significant pathologic findings consisted of marked edema of the lungs, and acute staphylococcal bronchopneumonia involving the inferior portion of the left upper lobe.

Case 4. A 62-year-old woman was admitted to Peter Bent Brigham Hospital for the second time, with complaints of periorbital, abdominal, and ankle swelling. Fourteen months prior to admission she was found to be hypertensive. Three weeks prior to admission she developed a sore throat with rhinorrhea and pain on swallowing, accompanied by headache and fever. Several days later she noted abdominal distention and moderate periorbital and pretibial edema. These symptoms were associated with moderate dyspnea, orthopnea, and cough. Both the volume and the frequency of her urine had diminished. Physical examination revealed marked periorbital and ankle edema. Blood pressure was 188/95 mm. Hg. The neck veins were distended and the patient was in severe congestive heart failure with cardiomegaly, pleural effusion, and ascites. The urine showed 3-plus proteinuria, many red blood cells, few white blood cells, and a few granular casts. Serum electrolyte levels were normal. Blood urea nitrogen and serum cholesterol were 61 and 284 mg./100 ml., respectively. The throat culture was negative for beta hemolytic streptococcus. Antistreptolysin titer, 500 Todd units; total serum protein, 5.9 gm./100 ml., with 2.6 gm./100 ml. albumin, and 3.3 gm./100 ml. globulin. Chest x-ray revealed cardiomegaly, right pleural effusion, and diffuse pulmonary congestion. In view of the typical history and an elevated antistreptolysin titer, the diagnosis of acute glomerulonephritis was made. The patient had an uneventful recovery, with a gradual fall in blood urea nitrogen to 22 mg./100 ml. The urine subsequently became negative, except for a trace of proteinuria.

Case 5. A 67-year-old woman was admitted to Massachusetts General Hospital because of increasing dyspnea of two weeks' duration. The patient appeared to be in good health until about four weeks prior to admission, when she developed an "influenza-like" syndrome, but without sore throat. On examination she was found to be markedly dyspneic. Blood pressure was 200/80 mm. Hg. Heart was moderately enlarged, and there were many fine inspiratory râles in both lung bases. Liver was enlarged but was not tender. There was marked edema of both legs. Urine was mahogany colored and showed 3-plus proteinuria. It was loaded with red blood cells, and contained a few white blood cells and many red blood cell casts. Serum electrolyte levels were unremarkable and blood nonprotein nitrogen was 34 mg./100 ml. A chest x-ray revealed bilateral pleural effusion. Throat culture was negative. However, the antistreptolysin titer was 625 Todd units. On the basis of her history, urinary findings, and an elevated antistreptolysin titer a diagnosis of acute glomerulonephritis was made. The patient improved markedly on a low salt diet and digitalis therapy and was discharged. A satisfactory recovery continued.

Case 6. A 66-year-old woman had had sore throat and fever three weeks prior to admission. Three days before admission she developed marked shortness of breath and cough. Dyspnea became worse and she was admitted to the emergency ward acutely ill, cyanotic, and obviously in pulmonary edema. Blood pressure was 210/100 mm. Hg. The heart was enlarged, and a diastolic gallop was audible. Breath sounds were diminished and râles were heard throughout both lung fields. X-ray of the chest revealed cardiomegaly and pulmonary changes consistent with pulmonary edema. Urinalysis showed 2-plus proteinuria, many red blood cells and white blood cells, rare hyaline casts but no red blood cell casts. Serum electrolyte levels were essentially normal. Nonprotein nitrogen was 40 mg./100 ml. Throat culture and antistreptolysin titer were not done. The admission diagnoses were myocardial infarction

and pulmonary edema. The patient responded satisfactorily to the usual treatment for pulmonary edema. Urine output was 210 ml. during the first 24 hours, increasing to 750,800, and 2,000 ml. during the subsequent 24 hour period. On the fourth hospital day her urine became grossly bloody. Urinalysis showed many red blood cell casts, in addition to other abnormalities noted previously. The patient's son was hospitalized concurrently with a diagnosis of acute glomerulonephritis. The patient improved and made an uneventful recovery on a low salt diet and digitalis therapy.

Case 7. A 67-year-old retired carpenter was admitted to Massachusetts General Hospital for the first time because of an exfoliative dermatitis of four months' duration. He showed a marked improvement on steroid therapy. Two weeks later the skin rash recurred, accompanied by dyspnea and orthopnea. Examination revealed bilateral pleural effusions. The heart was enlarged, and a loud systolic murmur was heard in the left parasternal area. The abdomen was distended with fluid, and the liver edge was palpable 5 cm. below the right costal margin. There was marked edema of both legs and of the scrotum. The urine was cloudy and showed 3-plus proteinuria. It was loaded with red blood cells, and contained few hyaline casts and doubly refractile bodies, but no red blood cell casts. Serum electrolyte levels were essentially normal, and serum cholesterol was 151 mg./100 ml. Total blood protein was 5.5 gm./100 ml., with globulin of 3.8 and albumin of 1.8 gm./100 ml. Throat culture showed no growth, and the antistreptolysin titer was 159 Todd units. A percutaneous kidney biopsy was performed which, on microscopic section, showed acute membranous glomerulonephritis. During hospitalization blood urea nitrogen increased from 23 to 145 mg./100 ml. Because of massive proteinuria and edema the patient was treated with steroids and a low salt diet. A remarkable diuresis followed, with impressive clinical improvement. The patient remained well following discharge from the hospital.

Discussion

Acute glomerulonephritis has been known classically as a disease of children and young adults. Furthermore, it has been maintained that acute glomerulonephritis occurs very rarely in patients in older age groups. The fallacy of this opinion is well illustrated by a recent report of 74 autopsied cases of glomerulonephritis in older adults. Of these 23 were classified anatomically as acute, and it was noted that the average age at necropsy in this group was 56.3 years.[5] Our report of seven cases of acute glomerulonephritis in patients well over 60 years of age re-emphasizes the point that the disease may occur in any age group.

Our patients manifested several interesting and perhaps atypical features. Table 1 outlines some of the salient aspects of their illness. Their ages ranged between 62 and 81 years. Four patients were male, three were female. The incidence of acute glomerulonephritis is reportedly greater in adult male patients.[6] The most common symptoms were dyspnea and edema. In one patient the illness was characterized by a sudden onset of total anuria. Another developed painless hematuria on two occasions before becoming anuric. All of the symptoms are rather atypical for acute glomerulonephritis in children or younger adults. In the latter groups the characteristic features are edema, hypertension, and abdominal pain.[7] It is of interest that only three patients had a history of preceding sore throat or upper respiratory infection. It is likely, however, that those patients in

whom the diagnosis of acute glomerulonephritis was not suspected were not carefully questioned in regard to the presence of antecedent sore throat. Careful bacteriologic examination of the throat was carried out in five patients, only one of whom showed a significant growth of beta hemolytic streptococcus. Those patients who had a preceding history of sore throat or upper respiratory infection dated it three to four weeks prior to the onset of their illness. These incidences probably represented the first attacks of acute glomerulonephritis rather than an acute exacerbation of a chronic process. The antistreptolysin titer was determined in three of these seven cases, all of which showed a marked elevation.

TABLE 1

Some Clinical Features of Acute Glomerulonephritis in Elderly Patients

Case	Age	Sex	Initial Symptoms	Initial Diagnosis	B.P. (mm. Hg)	Pulmonary Edema	Peripheral Edema	Beta Hemolytic Streptococcus	ASO Titer Todd Units	RBC Casts
1.	81	M	Anuria	Renal arterial occlusion	140/75	No	Yes	Yes	—	No
2.	79	M	Hematuria	Obstruction of upper urinary tract	172/100	No	Yes	—	—	No
3.	72	M	Dyspnea	Dehydration	160/80	No	Yes	No	—	No
4.	62	F	Dyspnea	Acute glomerulonephritis	185/95	Yes	Yes	No	500	No
5.	67	F	Dyspnea	Pulmonary embolism	200/80	Yes	Yes	No	635	Yes
6.	66	F	Dyspnea	Myocardial infarction	210/100	Yes	Yes	—	—	Yes
7.	67	M	Edema	Nephrotic syndrome	210/115	No	Yes	No	159	No

The simultaneous occurrence of acute glomerulonephritis in one of the patients and in her son indicates that the familial incidence of acute glomerulonephritis due to common exposure to nephritogenic beta hemolytic streptococcus probably exists in the aged. Therefore, older persons should be examined carefully for the organism and the proper prophylactic antimicrobial therapy instituted when a contact in the family develops beta hemolytic streptococcal infection.

Most of these patients developed hypertension during the course of their illness. Only two patients, however, were known to have some elevation of blood pressure before the onset of illness. As shown in Table 1, four of these patients were in pulmonary edema on admission and most of them showed some degree of congestive heart failure, ranging from moderate ankle edema to ascites and pleural effusion.

Examination of the urine invariably revealed protein and the presence of gross or microscopic hematuria. However, in only two cases were red blood cells casts noted. The infrequency of red blood cell casts in the urine of these patients may well be due to the fact that most of them were not suspected of having acute glomerulonephritis and perhaps no attempt was made to search for casts in the urine early in the course of the disease. Cystoscopy and retrograde pyelography were performed in two patients. It is interesting to note that these procedures were performed in the two oldest patients in whom the index of suspicion for an obstructive lesion of the urinary tract was justifiably high.

In only one case was a correct diagnosis considered on admission. A list of clinical diagnoses made initially appears in Table 1. Because all of these patients were in the older age group and probably had underlying generalized arteriosclerosis, occlusion of the renal arteries by a thrombus or an embolus was one of the most common diagnostic possibilities considered. In one of our patients, an 81-year-old man with only one kidney, the presence of diabetes mellitus and generalized arteriosclerosis, and the development of sudden anuria, led the admitting physician to consider the diagnosis of renal artery occlusion. A percutaneous renal biopsy revealed acute glomerulonephritis. In two cases obstruction of the urinary tract was suspected. It is important to realize that the obstructive lesions of the urinary tract and the occlusive processes of the renal arteries may in most circumstances be reversible and should be considered in all cases of acute renal failure.

In two cases the correct diagnosis was made by percutaneous renal biopsy. In three cases the correct diagnosis was made eventually during the course of hospitalization on the basis of additional history, clinical course, abnormal urinary sediments, positive throat culture for beta hemolytic streptococcus, and an elevated antistreptolysin titer. Post-mortem examination disclosed the correct diagnosis in the three remaining patients.

Three of the oldest patients in this group died in the hospital. The immediate cause of death was not established in one patient, but the other two succumbed to an overwhelming pulmonary infection. The strikingly high rate of mortality may be a consequence of various extrarenal complications, such as infection and cardiac arrhythmia, in patients with underlying chronic disease such as diabetes or arteriosclerotic heart disease. However, it is also possible that the natural history and the clinical course of acute glomerulonephritis in older patients may be quite different from those in children or young adults.

Summary

Seven cases of acute glomerulonephritis in elderly patients, ranging between 62 and 81 years of age, are presented. The most common presenting symptoms were dyspnea and edema, and several patients showed pul-

monary edema. Because of the atypical clinical features and the patients' ages an initial correct diagnosis of acute glomerulonephritis was considered in only one case. It is emphasized that acute glomerulonephritis is not limited to any age group. It occurs in older adults and not infrequently in patients 60 years of age or older.

SUMMARIO IN INTERLINGUA

Es opinate communmente que acute glomerulonephritis es un morbo de pueritia, adolescentia, e prime maturitate. Tamen, un numero considerabile de patientes de etates plus avantiate ha essite vidite con acute glomerulonephritis al Clinica Cardiorenal del Hospital Peter Bent Brigham e in le salas general del Hospital General de Massachusetts. Le presente communication reporta septe casos de acute glomerulonephritis in patientes de etates de sexanta annos o plus. Le etates del septe variava inter 62 e 81 annos. Quatro esseva masculos, tres feminas. Le symptomas le plus commun esseva dyspnea, edema, e oliguria. Solmente tres del patientes reportava antecedentes de mal de gurgite o de infection del vias supero-respiratori. Inter le culturationes de gurgite, effectuate in cinque casos, solmente un esseva positive pro streptococcos hemolytic beta. Le titro de antistreptolysina esseva determinate in tres patientes. In omne istes, illo esseva elevate. Le majoritate del patientes disveloppava hypertension. Le examine del urina revelava invariabilemente proteinuria e hematuria macro- o microscopic. Cylindros erythrocytic esseva identificate in duo casos. Le correcte diagnose esseva prendite in consideration al tempore del admission al hospital in solmente un del casos. Tres del patientes, illes del etates le plus avantiate, moriva al hospital. Le causa de morte le plus commun esseva un fulminante infection pulmonar. Le alte mortalitate in iste serie es possibilemente explicabile per le presentia de subjacente morbos chronic, como diabete mellite o morbo cardiac coronari.

Es sublineate le facto que acute glomerulonephritis non es restringite a specific gruppos de etate. Su presentia debe esser prendite in consideration etiam in patientes de etate avantiate.

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DIFFERENTIATION BETWEEN THYROID AND PARATHYROID CAUSES OF HYPERCALCEMIA *

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HYPERCALCEMIA in thyrotoxicosis was first reported largely as a medical curiosity.[1] Since then additional cases have been reported. The finding that serum calcium returns to normal after treatment of thyrotoxicosis suggests a causal relationship. The true incidence of hypercalcemia with thyrotoxicosis is not known, but this combination occurs with sufficient frequency to warrant consideration of hyperthyroidism in the differential diagnosis of hypercalcemia. Because the per cent of renal tubular reabsorption of phosphate is affected by parathyroid function, its determination is useful in the evaluation of hypercalcemia.[2] It is almost always low in hyperparathyroidism. In other causes of hypercalcemia—malignancy, vitamin D ingestion, sarcoid, milk-alkali syndrome, myeloma—it is only occasionally low. Because we found no systematic study of the tubular reabsorption of phosphate in thyrotoxicosis, with or without hypercalcemia, the present investigation of 27 thyrotoxic patients was undertaken.

Thirteen cases were studied at Charity Hospital, New Orleans, 13 at the University of California Medical Center, San Francisco, and one at Fort Miley Veterans Administration Hospital, San Francisco, using the University of California technic. All patients had clinical and laboratory evidence of hyperthyroidism, were untreated at the time of initial study, and were subsequently relieved of signs and symptoms by appropriate therapy. All patients had Graves' disease except the Fort Miley patient, who had a toxic adenoma. The information derived from these studies made possible the preoperative diagnosis of coexisting hyperthyroidism and hyperparathyroidism in two patients.

METHODS

Charity Hospital Technic: After an overnight fast, patients are hydrated until urine flow approximates 5 ml./min. Two-hour urine collections (7 to 9 a.m.) are made. Blood specimens are obtained at 8 a.m. Phosphorus (Gomori) and creatinine (Folin-Wu) determinations are done on each specimen of serum and urine. Serum calcium is measured at least once,

* Received for publication June 13, 1960.

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using the Coleman Jr. flame spectrophotometer. The tubular reabsorption of phosphate is calculated by the formula:

$$\% \text{ TRP} = \left[1 - \frac{\hat{UP} \times \hat{SCr}}{\hat{UCr} \times \hat{SP}}\right] \times 100$$

where $\hat{UP}$ is the urine phosphate, $\hat{SCr}$ the serum creatinine, $\hat{UCr}$ the urine creatinine, and $\hat{SP}$ the serum phosphorus concentrations.

University of California Technic: After three days on a diet free of milk and cheese, the patient is requested to have no food after 6 p.m., although water, tea, and black coffee without sugar are allowed. Urine voided from 8 p.m. to 8 a.m. is collected, and a fasting blood specimen is taken in the morning. Phosphorus is determined by the method of Taussky et al.,[3] creatinine by the method of Jaffe, and calcium by a modification of the method of MacIntyre.[4] With this method, 95% of normal subjects have serum calcium values between 4.80 and 5.65 mEq./L. The tubular reabsorption of phosphate is calculated from the above formula.

Results

The normal range for the tubular reabsorption of phosphate by the Charity Hospital technic is 76 to 91%. All 13 patients had normal serum calcium values when the tubular reabsorption of phosphate was determined. One patient (case 1) had hypercalcemia when first seen, but serum calcium spontaneously fell to normal before the tubular reabsorption of phosphate was determined. The tubular reabsorption of phosphate was in the normal range in three patients, and above normal in 10. Phosphate clearance correlated with it.

The normal range for the tubular reabsorption of phosphate by the University of California technic is 78 to 91% on a milk- and cheese-free diet. Of 13 patients studied by this method, only six had normal serum calcium levels; tubular reabsorption of phosphate was normal in five of the six, and was 94% in the other. The remaining eight patients all had hypercalcemia; tubular reabsorption of phosphate was normal in three, slightly high in one, and slightly low in one. We did not calculate it initially in one patient with hypercalcemia (case 3), because she had uremia. After she had taken 20 mg. of prednisone every eight hours for one week, the serum calcium level and the creatinine clearance were normal. The tubular reabsorption of phosphate was then normal also. Later, when hypercalcemia recurred without uremia, tubular reabsorption of phosphate was 92%. Two hypercalcemic patients (cases 8 and 9) had extremely low tubular reabsorption of phosphate (51% and 50%), which could not be raised normally by a diet containing 430 mg. of phosphate. Evaluation of the tubular reabsorption of phosphate sometimes requires measurement on a known phosphate intake, since unsuspected phosphate restriction may result in a value between 80

and 90% for hyperparathyroid patients. Under similar restriction normal subjects may conserve phosphate by raising the tubular reabsorption of phosphate to above 90%. There was no evidence that any of the other causes of low tubular reabsorption of phosphate was present in these these two patients.

Case Reports of Patients with Both Hyperthyroidism and Hyperparathyroidism

Case 8. A 68-year-old woman came to the University of California Medical Center on May 12, 1959. Her history included self-treatment of nodular goiter with iodine for 20 years; auricular fibrillation for 14 years; and passage of renal stones in 1951 and 1954. She had polyuria and polydipsia. The patient was confused and agitated, had a slight stare, and lid lag. The thyroid gland was multinodular and greatly enlarged. The liver was large and tender, the spleen palpable. Blood pressure was 200/90 mm. Hg, apical pulse 96 and fibrillating. Basal metabolic rate was plus 86%, serum calcium, 7.25 mEq./L., phosphorus, 3.7 mg.%, alkaline phosphatase, six Bodansky units, and tubular reabsorption of phosphate, 51%. After five days on a diet containing only 430 mg. of phosphate, serum phosphate fell from 3.9 to 2.5 mg./100 ml., and the tubular reabsorption of phosphate rose, but to only 84%. X-rays revealed only mild diffuse skeletal demineralization. A diagnosis of coexisting hyperthyroidism and hyperparathyroidism was made.

Table 1

Tubular Reabsorption of Phosphate in Uncomplicated Thyrotoxicosis

	No. of Cases	PBI μg./100 ml.	Serum Calcium mEq./L.	TRP %
Charity Hospital	13	16.5* (14.0–26.4)	4.90* (4.40–5.60)	94* (89–99)
University of California	6	12.4 (9.9–16.0)	5.40 (5.10–5.60)	88 (82–94)

* Figures given are means, with range in parentheses below.

The patient was given 150 mg. of propylthiouracil every eight hours and was digitalized, but when readmitted on July 31 was still moderately thyrotoxic. Serum calcium was 6.7 mEq./L.; tubular reabsorption of phosphate, 67%. The dose of propylthiouracil was increased to 300 mg. every eight hours, and phenobarbital and reserpine were given for sedation. On August 3 a parathyroid adenoma weighing 1.42 gm. was removed from the left lower pole of the thyroid, and 101.5 gm. of thyroid tissue were also removed. Four days after operation, serum calcium was 5.1 mEq./L., and tubular reabsorption of phosphate, 94%. In November the patient was euthyroid, and serum calcium was 5.2 mEq./L.

Case 9. A 65-year-old man was admitted to Fort Miley Veterans Administration Hospital in January, 1960, because of a solitary thyroid nodule. He had passed renal calculi in 1952 and 1955, and had had several episodes of renal colic in which stones were not found. He did not have polyuria or polydipsia. There were no symptoms or signs of thyrotoxicosis, but two determinations of the basal metabolic rate gave values of plus 21% and plus 22%. Protein-bound iodine was 11.8 μg./100 ml., and I^{131} uptake was localized in the nodule and amounted to 46% in 24 hours. Serum calcium was 6.25 mEq./L.; serum phosphate, 2 mg./100 ml.; tubular re-

TABLE 2

Data on Thyrotoxic Hypercalcemic Patients

Case	Date	Serum			Urine		TRP %	I^{131} Uptake %/24 hrs.	PBI μg./100 ml.	BMR %	Symptoms Possibly due to Hypercalcemia
		Calcium mEq./L.	Phosphorus mg./100 ml.	Creatinine mg./100 ml.	Phosphorus mg./12 hrs.	Creatinine mg./12 hrs.					
1	12/4/58[1]	6.10						55	16.4		None
	5/14/59	5.40	3.0	1.1	2.3[2]	138	99				
2	10/18/57	5.90	5.0	0.6	361.	361	88	86	19.1		Anorexia, nausea, constipation, abdominal pain, polydipsia, polyuria
	5/1/59[3]	5.50	4.7						5.9		
3	9/5/58	7.00	3.7	2.4	341.	675					Nausea, constipation, dry mouth
	9/21/58[4]	5.10	2.9	1.3	233.	619	84				
	4/15/59	6.10	3.4	1.0	230.	815	92	50			
	3/29/60[5]	5.35	3.6	1.3	415.	775	81	32			
4	1/4/59	6.50	4.2	0.8	645.	520	76	58 (5 hrs.)	20.0	+72	Thirst, polyuria, "cinders in eyes"
	3/29/60[3]	5.60	4.2	1.0	600.	1450	90				
5	1/11/60	5.75	4.1	0.8	120.	141	83	47 (5 hrs.)	11.7		None
	3/16/60[3]	5.10									
6	2/8/60	6.00	3.8	0.6	556.	435	81	81	11.6	+39	Nocturia
	3/3/60[3]	5.20	3.8	0.8	105.	177	87				
7	3/18/60	5.70	5.6	0.9	305.	840	94	84	15.9	+40	None
	5/6/60[6]	5.30	3.7	0.9						+4	
	Combined Hyperthyroidism and Hyperparathyroidism										
8	5/19/59	7.25	2.4	0.8	399.	270	51			+86	See case report
	5/27/59[7]	6.80	2.5	0.9	246.	435	84				
	8/7/59[8]	5.10	3.7	1.1	64.	341	94				
9	2/29/60	6.25	2.0	1.2	534.	640	50	46	11.8	+21	See case report
	3/23/60[8]	5.35	3.4	1.1	160.	522	91				

1. Charity Hospital patient.
2. Two-hour urine collection.
3. After subtotal thyroidectomy.
4. After prednisone therapy.
5. After I^{131} therapy.
6. After diiodothyroacetic acid.
7. After 430 mg. phosphorus diet.
8. After adenoma removal and subtotal thyroidectomy.

absorption of phosphate, 50%. A diagnosis of hyperfunctioning thyroid adenoma, and hyperparathyroidism was made. At operation a right-sided thyroid adenoma, with a diameter of 6.3 cm., and an adenoma of the left superior parathyroid gland, 2 by 1.5 cm., were removed. After operation, serum calcium was 5.35 mEq./L.; serum phosphate, 3.4 mg./100 ml.; tubular reabsorption of phosphate, 91%. Basal metabolic rate was minus 1%, and protein-bound iodine was 2.2 μg./100 ml.

Discussion

In 1929 Aub and his associates [5] established that hyperfunction of the thyroid gland is associated with increased excretion of calcium and phosphorus. They, and others since, have demonstrated that thyrotoxicosis may result in hypercalciuria and negative phosphate balance.[6, 7] Logan et al.[8] found that administration of desiccated thyroid to dogs caused a tenfold rise in urinary calcium without change in serum calcium. Using the balance technic, Aub [5] found that the observed phosphate loss was equal to the amount made available by protein catabolism, plus the amount released from bone crystal as a passive partner of calcium. Other investigators have been unable to confirm such a correlation between calcium, phosphorus, and nitrogen balances in either spontaneous [6] or induced [9] thyrotoxicosis.

It is now clear that bone participates in the general increase in metabolism of hyperthyroidism. It has been shown that bone formation increases in the presence of hyperthyroidism,[10, 11] but, because there is a net loss of bone minerals, bone resorption is probably increased more than its formation. This resorption of bone can be severe enough to cause pathologic fractures,[12] and may simulate metastatic malignancy of bone [12, 13] and osteitis fibrosa generalisata.[14] Puppel [13] has urged administration of calcium and phosphorus in the treatment of hyperthyroidism.

As a rule, the serum calcium level is normal in hyperthyroidism, but hypercalcemia has been documented in 19 cases.[1, 15–24] Our series adds seven cases, four of whom had symptoms that could be related to hypercalcemia. In all cases, the serum calcium level returned to normal when thyrotoxicosis was treated. There was no apparent correlation between the degree of thyroid overfunction assessed clinically or by laboratory tests and the development of hypercalcemia.

One of our patients (case 3) had minimal azotemia, which cleared when the serum calcium was reduced by prednisone. This change preceded treatment of the thyrotoxicosis. König and Gubler [24] also administered prednisone to a thyrotoxic hypercalcemic patient. The serum calcium level fell from 14.7 to 12.6 mg./100 ml., and uremia diminished. Since during the same period the patient was hydrated and was taking methimazole, the cause of the fall in serum calcium and urea levels is not clear. Others [17, 20, 23] have reported a reversal of azotemia and hypercalcemia when hyperthyroidism was corrected.

It has been suggested that the parathyroid glands are involved in the calcium and phosphorus wasting of Graves' disease.[25, 26] The frequent lack

of correlation between the degree of hypermetabolism and the amount of mineral loss has prompted Hansman and Wilson [26] to postulate that associated hyperparathyroidism is responsible for the calcium and phosphorus losses. Beaumont et al.[27] also doubted the direct thyroid origin of these changes, and Robertson [7] suggested a renal mechanism as the cause. This question would be answered if parathyroid hormone in blood or urine could be directly measured, but no present method is sufficiently sensitive. The tubular reabsorption of phosphate reflects the phosphate diuretic effect of parathyroid hormone, and its use as an indirect assay of parathyroid activity has been suggested.[28] Beisel and his associates [29] found that intravenous administration of very large doses of tri-iodothyronine to dogs caused a fall in the tubular reabsorption of phosphate. The tubular reabsorption of phosphate was low in the thyrotoxic patient reported by Epstein et al.[23] but its significance is difficult to evaluate because the patient was uremic. These two reports of low tubular reabsorption of phosphate associated with excessive thyroid hormone support Hansman's and Wilson's contention.[26] However, hyperparathyroidism could not have been responsible for the negative calcium and phosphorus balances in the patient with coexisting hypoparathyroidism and hyperthyroidism reported by Cope and Donaldson.[30] Aub et al.[31] raised the serum calcium level in hypoparathyroid patients by giving them thyroxine. McCullagh [32] found no constant histologic evidence of hyperplasia in the parathyroids of hyperthyroid patients. The ability of corticoids to lower the blood calcium in one of our patients with hypercalcemia also is evidence against the Hansman and Wilson theory, since the hypercalcemia of hyperparathyroidism is usually resistant to corticoids.[33, 34] Finally, the results of the test of tubular reabsorption of phosphate in our series do not substantiate the presence of hyperparathyroidism in most cases of thyrotoxicosis. We found the values for tubular reabsorption of phosphate to be normal or elevated in all but three of our patients. Two of the three proved to have parathyroid adenomas. The third showed only a slightly low tubular reabsorption of phosphate, and after correction of thyrotoxicosis, it and the serum calcium were normal. While the tubular reabsorption of phosphate appears to reflect parathyroid function, it can also be altered by changing the dietary content of phosphorus, by ingestion of vitamin D, and by renal infection and other causes of renal tubular damage. None of these factors existed in our patients.

If one accepts Aub's concept that thyroid induces bone resorption directly, the body would, in effect, be receiving an endogenous infusion of calcium and phosphorus in thyrotoxicosis. Intravenous calcium infusion usually causes an increase in the tubular reabsorption of phosphate,[35] and phosphate infusion causes a fall.[36] It has been suggested that these effects are mediated by the parathyroid glands,[37] but this has not been established. The effect of thyrotoxicosis on the tubular reabsorption of phosphate would be the sum of the effect of calcium and phosphate liberated by thyroid hor-

mone and the state of parathyroid activity. This may explain its variation in some of our cases. Calcium and phosphorus metabolism may also be affected by normal amounts of thyroid hormone. Krane et al.[10] reported that calcium deposition in bone is more rapid in normal subjects than in myxedematous subjects.

In cases 8 and 9 a consistently low tubular reabsorption of phosphate, with no other apparent cause, permitted a correct diagnosis of hyperparathyroidism in the presence of thyrotoxicosis and hypercalcemia. We could find in the literature only six similar, documented cases of coexisting hyperthyroidism and hyperparathyroidism.[15, 38-42] In only one of these [38] was the tubular reabsorption of phosphate measured and, as in our cases, it was depressed.

It is clear that when thyrotoxicosis complicated by hypercalcemia is accompanied by a persistently low tubular reabsorption of phosphate, another cause for the hypercalcemia, such as hyperparathyroidism, must be sought.

Summary

To evaluate the hypercalcemia sometimes associated with thyrotoxicosis, the percentage of tubular reabsorption of phosphate was determined in 27 thyrotoxic patients. This was done by two-hour urine collections at Charity Hospital, New Orleans, and by a 12-hour overnight collection at the University of California Medical Center.

The tubular reabsorption of phosphate was normal or high in 24 of the 27 patients. Nine patients had hypercalcemia, and among these were the three whose tubular reabsorption of phosphate was low. In two with extremely low values for tubular reabsorption of phosphate (51% and 50%), hyperparathyroidism was diagnosed preoperatively, and both patients had parathyroid adenomas. The third patient had a borderline low tubular reabsorption of phosphate of 76%, and after therapy for thyrotoxicosis his serum calcium level and tubular reabsorption of phosphate were normal.

Administration of prednisone to one thyrotoxic patient with hypercalcemia and uremia resulted in normal values for serum calcium and creatinine.

Summario in Interlingua

Le ver incidentia de hypercalciemia con thyrotoxicosis non es cognoscite, sed iste combination occurre con frequentias sufficientemente marcate pro justificar le consideration de hyperthyroidismo in le diagnose de hypercalciemia. Proque le procentage del reabsorption tubular de phosphato es afficite per le function parathyroide, le determination de iste parametro es utile in le evalutation de hypercalciemia. Le reabsorption tubular de phosphato es quasi semper basse in casos de hyperparathyroidismo. In casos con altere causas del hypercalciemia—malignitate, ingestion de vitamina D, sarcoide, syndrome de alkali de lacte, myeloma—illo es basse solo occasionalmente. Viste que nos non poteva trovar un studio systematic del reabsorption tubular de phosphato in casos de thyrotoxicosis—sin o con hypercalciemia—le presente investigation de 27 patientes thyrotoxic esseva interprendite.

Esseva usate duo methodos pro determinar le procentage del reabsorption tubular de phosphato. In le un, le patientes—post jejuno transnocturne—esseva hydratate usque le fluxo de urina esseva approximativemente 5 ml/min. Duo collectiones de duo horas de urina esseva facite (7 a 9 e 9 a 11 horas). Specimens de sanguine esseva obtenite a 8, 9, e 10 horas del matino. Un micre repasto esseva fornite a 9 horas. Le area del valores normal que iste methodo indicava pro le reabsorption tubular de phosphato es illo ab 76 ad 91 pro cento. In le altere methodo, urina vacuate per le patiente inter 20 e 8 horas esseva colligite post que le dieta del patiente habeva essite libere de lacte e caseo durante tres dies. Un specimen de sanguine de matino esseva obtenite in stato jejun. Secundo iste methodo, le area del valores normal pro le reabsorption tubular de phosphato esseva ab 78 ad 91 pro cento.

Omne le patientes exhibiva signos clinic e laboratorial de hyperthyroidismo; omnes habeva recipite nulle tractamento al tempore del studio initial; e omnes esseva alleviate subsequentemente ab lor signos e symptomas per un therapia appropriate.

Como regula general, le nivello seral de calcium es normal in hyperthyroidismo, sed le presentia de hypercalciemia se trova documentate in 19 previe casos. Nostre serie adde septe casos a ille total, le majoritate con symptomas que poteva esser ponite in relation con hypercalciemia. In omnes, le nivello seral de calcium retornava al norma quando le thyrotoxicosis esseva tractate. Esseva notate nulle apparente correlation inter le grado de hyperfunction thyroidic evalutate clinicamente o per tests laboratorial e le disveloppamento de hypercalciemia. Le administration de prednisona a un patiente thyrotoxic con hypercalciemia e uremia resultava in valores normal pro calcium e creatinina del sero.

Le valores pro le reabsorption tubular de phosphato esseva normal o elevate in 24 inter 27 patientes. In duo, le reabsorption tubular de phosphato esseva bassissime. In ambes, le suspicion de adenoma parathyroide esseva confirmate al operation. Un del patientes monstrava un solo levemente reducite reabsorption tubular de phosphato, e post le correction del thyrotoxicosis in iste caso, ille valor e le valor del calcium seral esseva normal. Durante que il pare que le reabsorption tubular de phosphato reflecte le function parathyroide, il es etiam possibile alterar lo per alterar le contento de phosphoro in le dieta, per le ingestion de vitamina D, e per infection renal e altere causas de injuria in le tubulos renal. Nulle tal factor esseva presente in nostre patientes.

Il es clar que—quando thyrotoxicosis complicate per hypercalciemia es accompaniate de un persistentemente basse reabsorption tubular de phosphato—un altere causa del hypercalciemia, per exemplo hyperparathyroidismo, debe esser trovate.

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HEPATOMA: CLINICAL EXPERIENCES WITH A FREQUENTLY BIZARRE TUMOR*

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Classic descriptions of primary liver cancer suggest that it presents most often with symptoms such as progressive emaciation, physical deterioration, pain in the right upper quadrant, an enlarging nodular liver, jaundice, and ascites in a patient with alcoholic cirrhosis. There is infrequent emphasis in the literature on the protean and polymorphic nature of this tumor which, because of the anatomic opportunity offered by the liver, may present in a number of bizarre clinical forms. Such case material is frequently chosen for clinical pathologic exercises because hepatoma is often a surprising finding in the undiagnosed fatal case. We have been impressed by the lack of emphasis in the general clinical literature on what have been classified as "atypical cases," and would suggest that the tumor appears more often than is realized in various guises and in unexpected and bizarre syndromes. Heretofore hepatoma has been considered almost exclusively as a complication of alcoholic cirrhosis, but contemporary studies of the natural history and pathology of postinfectious hepatitis [1, 2] justify a re-evaluation of this notion. Seventeen cases of hepatoma illustrating the diverse clinical syndromes that may confront the diagnostician are summarized in Table 1. Nine cases exhibiting useful diagnostic clues are discussed in some detail.

Case Reports

Case 1. Hematobilia and hemoperitoneum. On December 7, 1953, a 29-year-old white male was admitted with a five-day history of epigastric pain, nausea, vomiting, and anorexia. He stated that his previous health had been excellent, except for jaundice as a child. This was of unknown etiology and duration. Examination revealed only right upper quadrant tenderness and muscle guarding. On the second hospital day, he became icteric, passed dark colored urine, and had marked abdominal pain. The direct acting serum bilirubin was 12 mg.% and there was a leukocytosis. There followed a five-day course of spiking fever, chills, and increasing jaundice, then a rapid diminution of all symptoms. No antibiotics were administered. Oral cholecystogram, upper gastrointestinal studies, and cone-down films of the gallbladder region were all normal. Except for occult blood in the stool he was asymptomatic, and was discharged on December 20.

The patient was readmitted on April 6, 1954 after having been asymptomatic for four months. He complained of right upper quadrant pain and tenderness, fever, and jaundice of 24 hours' duration. He was extremely ill with an acute abdominal

* Received for publication July 27, 1960.

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TABLE 1

Summary of Hepatoma Cases Presenting Atypical Clinical Findings

Case No.	Presenting Clinical Picture	Age	Sex	Tumor Cell Type	Tumor Spread at Autopsy
1.	Acute Abdomen A. With hemorrhage outstanding	29	M	H-C*	Visceral and parietal peritoneum, periportal and mesenteric nodes, diaphragm, left adrenal gland, right cerebral hemisphere.
2.	Acute Abdomen A. With hemorrhage outstanding	44	M	H-C	Both lungs, spleen, both kidneys, splenic pedicle, stomach wall, left adrenal, left renal pedicle, emboli in glomerular tufts.
3.	Acute Abdomen A. With hemorrhage outstanding	45	M	H-C	Right hemidiaphragm, necrotic rupture of liver surface with hemorrhage.
4.	B. As acute cholecystitis	51	M	H-C	Portal lymph nodes, intravascular in lungs, portal vein radicles, Virchow's node.
5.	C. As fever, unknown origin	54	F	C-C†	Multiple intrahepatic, periportal and peripancreatic nodes filled with metastases.
6.	Acute Hepatic Decompensation	65	M	H-C	Diffuse liver involvement by carcinoma, bilateral lung and adrenal gland metastases.
7.	Chiari's Syndrome	37	M	H-C	Periportal nodes, occlusion of hepatic veins by tumor masses.
8.	Chest Disease A. With bloody pleural effusion	66	M	H-C	Left lung, ribs and pleura, mediastinal nodes.
9.	Chest Disease A. With bloody pleural effusion	65	F	C-C	Portal nodes, metastases to both lungs and pleura.
10.	Chest Disease A. With bloody pleural effusion	58	M	H-C	Both lungs, peritoneum, inferior vena cava, tumor emboli in right auricle and pulmonary artery.
11.	Chest Disease A. With bloody pleural effusion	62	M	H-C	Massive involvement of both lungs and pleura.
12.	B. Dyspnea, dysphagia, and clavicular mass	74	M	H-C	Left clavicle, left adrenal, both lungs, periportal nodes, peritoneum.
13.	Systolic Bruit Over Liver	22	F	H-C	No autopsy.
14.	Systolic Bruit Over Liver	74	M	H-C	Both lungs, portal vein, venous collaterals around xiphoid, right hemidiaphragm.

* H-C—hepatocellular. † C-C—cholangiocellular.

disease and was prepared for surgery as rapidly as possible. At exploratory laparotomy, the gall-bladder was distended with blood, the common duct was clear, and the abdomen was otherwise normal. A cholecystectomy was performed and the common duct was drained with a T-tube. The postoperative course was complicated by bloody discharge from the T-tube for 10 days, but this cleared, and on April 19 a choledochogram was normal. The pathologic report was "acute hemorrhagic cholecystitis," and the patient was discharged as being improved.

The third admission was on August 4, 1954. The patient had been asymptomatic since his previous discharge until two weeks earlier, when he experienced black tarry stools, abdominal pain, nausea, and vomiting. Upon admission, he had signs and symptoms of abdominal obstruction, but these abated completely and he was discharged as being asymptomatic. The fourth admission was on August 15, 1954, when he appeared with evidence of a ruptured intra-abdominal viscus. Laparotomy

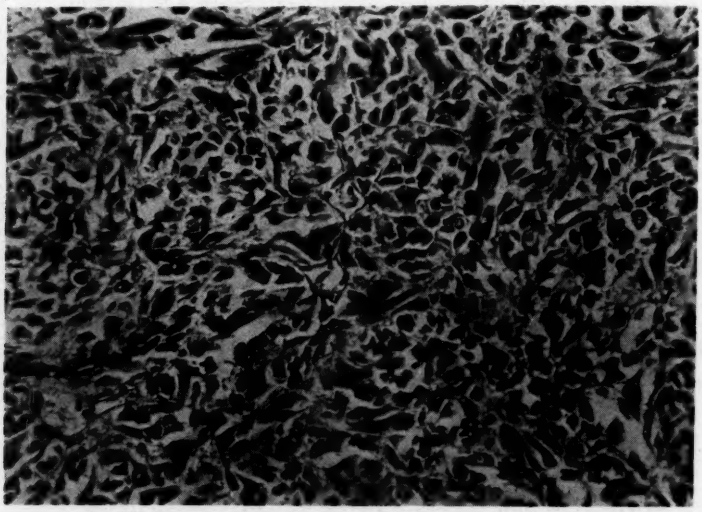

FIG. 1. Photomicrograph of the liver in case 1. There is almost total replacement of the liver parenchyma by hepatoma cells which are spindle shaped in many instances, suggesting "psuedo-sarcoma." × 340.

revealed necrotic tumor invasion of the gastrohepatic vessels and tumor nodules in the liver, mesocolon, and ileum. Biopsy specimens proved the lesion to be hepatocellular carcinoma.

The patient survived the operation but suffered an intraperitoneal hemorrhage on November 6, 1954 and died in shock. At autopsy there was a mass 14 by 10 cm. in the right lobe of the liver invading the intrahepatic portion of the right hepatic duct. Blood was seen to flow from vessels in the tumor mass and down into the duct. No other site of bleeding could be found to explain the melena or hematobilia in this man's course.

Case 2. Hemoperitoneum. In June, 1958, a 44-year-old Hawaiian male with a history of high alcohol intake was admitted with epigastric pain, bloody diarrhea, weakness, vomiting, and diaphoresis of 24 hours' duration. On admission, he was icteric, febrile, in mild shock, and there were bloody ascites and peripheral edema. The bromsulfalein retention was 18%; the prothrombin time was 40% of normal;

his hemoglobin was 5.4 gm.%. He had marked abdominal distention, no bowel sounds, and extreme tenderness and muscle guarding over the entire abdomen. The state of shock was treated with intravenous blood and colloids, but the patient failed to respond, and over the next 24 hours developed a cardiac arrhythmia and died suddenly. Autopsy diagnosis was hepatocellular carcinoma with tumor invasion of the gastrohepatic ligament and massive intra-abdominal hemorrhage.

Case 4. Acute cholecystitis syndrome. A 51-year-old white male had been completely well until September 1, 1950, when he was suddenly stricken with acute upper abdominal pain which penetrated through to the right scapula. The pain persisted without other symptoms for two weeks. On admission, the vital signs were normal. The physical examination was characterized by right epigastric area tenderness and muscle guarding. The patient was felt to have acute cholecystitis until the second hospital day, when one examiner palpated a hard, fixed 2 cm. Virchow's node. This prompted a diagnosis of intra-abdominal malignancy and an exploratory laparotomy was performed. At operation the liver was infiltrated with hard, yellow nodules and the portal lymph nodes were grossly involved with tumor. Biopsies were taken and the abdomen was closed. The postoperative course ended in coma and death five days later.

Autopsy demonstrated a hepatic cell carcinoma with metastases to portal nodes, to Virchow's nodes, and tumor thrombosis of the portal vein as well as vascular tumor emboli in both lungs.

Case 5. Fever with necrotic tumor abscess. A 54-year-old white female who had an enterocele repaired one month previously was admitted complaining of right upper quadrant pain, tenderness, nausea, vomiting, and fever of five days' duration. Chloromycetin and intravenous fluids relieved the symptoms for 10 days. An oral cholecystogram failed to demonstrate the gall-gladder. She was discharged, asymptomatic, to be followed as an outpatient. One week later she experienced recurrent fever and right upper quadrant pain with leukocytosis and an elevated erythrocyte sedimentation rate to 89 mm./min., despite chloromycetin and other symptomatic therapy. An exploratory laparotomy was performed on December 6, 1956. A choledochoduodenal fistula was closed. An abscess was cultured and drained, with *Escherichia coli* being cultured from it. The postoperative course was one of continued drainage from the abscess site, fever, and, later, jaundice. She steadily deteriorated despite antibiotics and further drainage of the liver abscess, and died on May 24, 1957.

At autopsy, there was found a cholangiocellular hepatoma (Figure 2), with multiple intra- and extrahepatic metastases. The abscess that had been drained was part of a large necrotic tumor mass.

Case 6. Diffuse hepatoma with acute hepatic and renal failure. A 65-year-old white male was admitted with complaints of jaundice of one week's duration and fatigue and lassitude for six weeks. He died in a state of coma 11 days after entry. He had been in his usual good health during a Caribbean cruise five weeks previously, during which time he had eaten sporadically and had drunk considerable rum. After the cruise he noted fatigue, lassitude, jaundice, and abdominal distention. Past history revealed no known stigmata of liver disease although he admitted to a large intake of alcohol for many years. At admission, the vital signs were normal, he was alert, slightly jaundiced, had "liver palms," spider angiomata of face and neck, slight cardiomegaly, and a small left pleural effusion. The total size of the liver was estimated to be 2½ times normal. It had a rounded, tender edge which descended to the umbilicus, and the left lobe appeared larger than the right. Pertinent laboratory findings: BUN of 34 mg.%, normal serum electrolytes and proteins, prothrombin time, 30% of normal, normal cephalin flocculation and thymol turbidity reactions, total serum bilirubin, 30 mg.%, with 21 mg.% direct reacting, an alkaline phosphatase activity of 25 King-Armstrong units, serum glutamic oxalacetic trans-

aminase activity, 182 units, and occult blood present in the stool. During the 11 days of hospitalization, physical findings were essentially unchanged, but he showed persistently tarry stools, hematemesis, and rapid deterioration, with the terminal course featuring increasing confusion, slurring speech, muscular movements resembling a flapping tremor, but no fever. On the eleventh day, he lapsed into coma and died quietly. At autopsy a diffuse hepatocellular carcinoma involved all of the liver substance, and there was hepatomegaly to three times normal size. The liver cells that remained showed marked fatty metamorphosis (Figure 3). There was no evidence of cirrhosis.

Case 7. Chiari's syndrome. A 37-year-old white male was admitted on August 21, 1953 complaining of epigastric soreness, pain in the left arm, gas, belching, and flatus of three months' duration, with one week of marked pain in the upper right quadrant of the abdomen. Past history was otherwise negative and admission

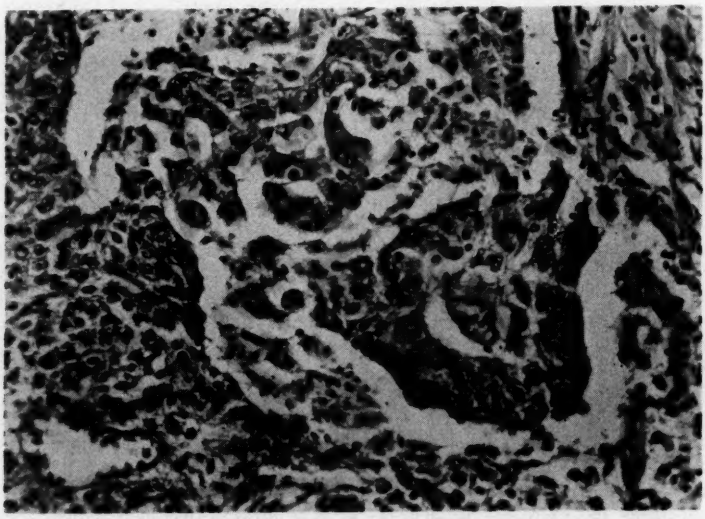

FIG. 2. Photomicrograph of the liver in case 5. A high degree of malignancy is seen with extensive invasion of the liver substance, numerous mitotic figures, and the formation of new bile duct structures typical of cholangiocellular hepatoma. × 340.

laboratory studies were within normal limits. An oral cholecystogram demonstrated filling of the gall-gladder. His condition remained unchanged and an exploratory laparotomy was performed on the third hospital day. There was one liter of straw-colored fluid in the abdominal cavity. This was negative for malignant cells. The liver was enlarged to twice normal size, and there were multiple small black areas of hemorrhage beneath the capsule. Postoperatively the patient did well. Serum electrolytes, proteins, cephalin flocculation, and thymol turbidity tests were all normal, but his ascites persisted (without edema). He was discharged feeling well. On October 7, 1953 an upper gastrointestinal series was normal. The ascites rapidly reaccumulated despite multiple abdominal paracenteses which yielded straw-colored fluid. The liver was found to be huge with a blunted, rounded edge, and splenomegaly was evident. It was proposed that the liver enlargement, with progressive portal hypertension and some disturbance of liver function, suggested an occlusion of the

hepatic veins, probably of a thrombotic nature. Ascitic fluid reaccumulation persisted despite albumin therapy. He was again explored, a portacaval shunt was established, and a liver biopsy was taken. He died quietly one week later.

Autopsy disclosed multiple large nodules within the liver parenchyma which consisted of hepatocellular carcinoma. There were metastases to the porta hepatis, and subtotal obstruction of the hepatic vein by tumor.

Case 8. Malignant pleural effusion with subsequent empyema and a protracted course. This 66-year-old white male was first admitted on November 29, 1946, with a chief complaint of increasing dyspnea of two months' duration. Systemic review, past history, and family history were noncontributory. On admission, the vital signs were normal, and physical findings were those classic for a left pleural effusion. On palpation a nontender, smooth liver edge was felt 4 cm. below the right costal margin. During the next 10 days, six thoracenteses were performed,

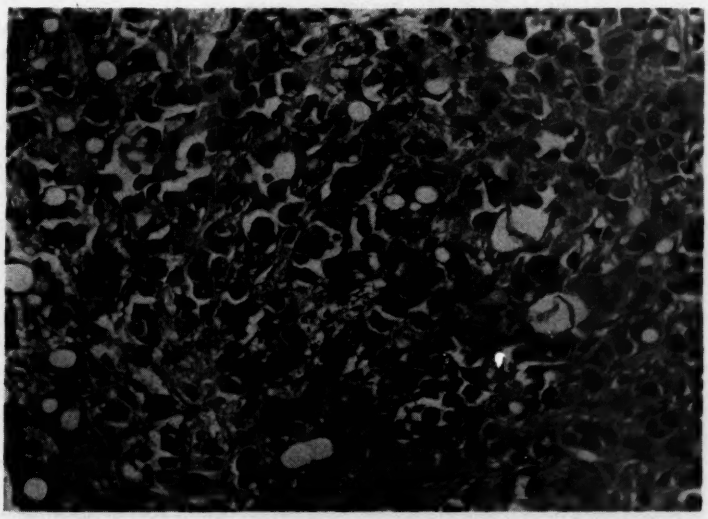

FIG. 3. Photomicrograph of liver in case 6. A small portion of identifiable hepatic parenchyma may be seen in the lower right corner. The liver was almost totally replaced by a widely invasive hepatocellular hepatoma. Fatty degeneration is seen, both in the remaining liver parenchyma and throughout the invaded area. × 340.

with the removal of seven liters of bloody fluid. This was repeatedly negative for malignant cells and acid-fast organisms, but hemolytic *Staphylococcus aureus* was cultured from it. The patient did well and was discharged as improved on December 10, 1946.

His second admission was on April 4, 1947 after one week of increasing production of yellow sputum and shortness of breath, with onset of drainage of purulent material from the left hemithorax. This area was surgically drained and the patient was discharged as improved on April 10.

The third admission was on August 8, 1947. He had gradually deteriorated since his previous admission, and complained of abdominal swelling, edema of the legs, increasing shortness of breath, and persistent drainage from the fistula. While receiving x-ray therapy to the left chest for relief of pain, he suddenly became moribund and died.

Autopsy findings: Primary hepatocellular carcinoma, with multiple metastases to the left lung, the mediastinal nodes, the pleura and the ribs of the left hemithorax; persistence of the empyema was noted in an area of tumor necrosis.

Case 12. Dysphagia, dyspnea, and large clavicular metastasis. A 74-year-old Italian male was admitted with a chief complaint of dysphagia of four months' duration, when he had first noted discomfort after swallowing solid food. He had since lost 18 pounds, and his swallowing difficulty had become more painful in the last two weeks. Systemic review and past medical history were unremarkable except for a heavy consumption of wine throughout most of his life.

On admission, the abdomen was distended and a fluid wave was detected. A 5 by 5 cm. irregular, hard mass was fixed to the left clavicle, scapula, and overlying skin, and there was 2-plus pitting edema of the legs. A paracentesis was performed and 300 ml. of yellow fluid were removed. The fluid was negative for tumor cells. He was severely emaciated and the major therapy attempted was feeding. On the eighth hospital day he suddenly became unresponsive and died.

Autopsy disclosed hepatocellular carcinoma. There was extensive necrosis of the primary tumor masses in the liver, producing exsanguinating intra-abdominal hemorrhage. The large clavicular mass was found to be metastatic tumor, and there were massive esophageal varices.

Case 13. Systolic bruit over an upper abdominal mass. A 22-year-old white housewife was admitted on April 13, 1953, complaining of abdominal swelling of five months' duration. In 1951, she had been slightly jaundiced and a diagnosis of infectious mononucleosis had been made elsewhere (criteria unknown). She felt well until early 1952, when she experienced intermittent diarrhea and constipation. During January, 1953, she had an influenza-like illness with a 15-pound weight loss, but she had regained nine pounds by the time of her admission. Past history and systemic review disclosed that she had menstruated regularly until amenorrhea developed during the past three months. Admission examination was within normal limits except for the abdomen, which was markedly distended. Palpation revealed a large, dome-shaped mass in the right upper quadrant which extended across the midline. At the center of the mass a tender, small nodule was felt, and a smooth, firm liver edge was palpable below the umbilicus in the midline. The spleen was not palpable, but it was enlarged to percussion and there was a loud systolic bruit heard directly over the mass in the right upper quadrant. Chest and abdominal x-rays were unrevealing. Extensive laboratory examination showed the only gross abnormality to be a prothrombin time of 40% of normal. Stool studies for blood, parasites, and ova were negative. Because of the mass and the bruit a neoplasm was suspected, and an exploratory laparotomy was performed. At operation, the liver was huge, especially the right lobe, and consisted of diffusely spreading multinodular tumor. Biopsies revealed this to be a primary hepatocellular carcinoma. The patient died at home several months later. No autopsy was performed.

Discussion

Tumors of large solid organs may remain clinically obscure until they reach a considerable size, extend to the surface, cause symptoms in adjacent organs, or metastasize. As the largest solid organ in the body, the liver offers special difficulties to the diagnostician until tumors growing within it reach a huge size. Because of its large mass and surface area, the liver is contiguous to a number of viscera and membranes, offering to a growing intrahepatic carcinoma an enormous area for presentation, ranging from the chest and pleural structures above to the abdominal parietes and abdomi-

nal viscera below. In spite of this, primary carcinoma of the liver is rarely an early diagnosis and is always a difficult one.

Berman,[3] using an arbitrary grouping based on the presenting clinical picture, attempted a clinical classification of hepatic carcinoma. Five clinical groups were thus defined, and Popper[4] has recently added a sixth. Group I cases are those of a typical liver cancer—rapid progression in a patient who has a large, tender, nodular liver, often associated with jaundice and ascites. Group II (Popper), the commonest clinical pattern, includes those cases of unexplained deterioration in an established case of cirrhosis showing splenomegaly, ascites, pain and rapid, tender enlargement of the liver associated with a detectable venous hum or bruit and some deterioration of hepatic function. The final four groups of less common occurrence appear as Group III, acute abdominal emergencies arising from hemorrhage from a carcinomatous nodule or blood vessel erosion; Group IV, cases with acute febrile illness associated with severe, sudden pain and tenderness over the liver and symptomatic manifestations of toxemia suggesting abscess; Group

TABLE 2

Case Frequency as to Clinical Type in 47 Cases of Hepatoma

Clinical Type (Berman-Popper classification—see text)	No. of Hepatoma Cases	Per Cent of Total Cases
I. Typical liver cancer	17	36%
II. Cirrhosis with rapid, unexplained deterioration	11	24%
III. "Atypical clinical course"	14	30%
IV. —	—	—
V. —	—	—
VI. Occult Hepatoma	5	10%
Total cases	47	100%

V, cases with signs and symptoms of metastases to distant sites; and Group VI, cases in which occult cancer complicates other diseases found incidentally at operation, biopsy, or autopsy. While our experiences are in general agreement with this classification, the atypical cases have been impressive both in frequency (30% of our series) and manner of clinical presentation. This prompted a review of 47 cases from five hospitals in Portland, Oregon,* which are classified as to clinical type in Table 2.

It is our purpose to emphasize the atypical findings which may arise from bizarre metastatic patterns and curious intrahepatic growth characteristics, and to stress the more frequent occurrence of such findings as well as their use in the diagnosis of obscure cases.

Nodular Growth of Tumor: Rapid enlargement of the liver is a common sign of hepatoma and tumor nodules may grow to huge size. The growth

* University of Oregon Medical School Teaching Hospital, Multnomah County Hospital, United States Veterans Administration Hospital, St. Vincent's Hospital, and Good Samaritan Hospital.

of isolated tumor nodules may lead to compression of adjacent organs, producing useful diagnostic clues, such as Chiari's syndrome with occlusion of the hepatic veins, or a systolic bruit when contiguous to large vessels. Although Chiari's syndrome resulting from intravascular tumor occlusion has been reported,[3, 5, 6] the hepatic vein obstruction in case 7 was due to impingement of a tumor nodule, with subsequent hepatomegaly, progressive portal hypertension, and some alteration of liver function. Case 13, who had a loud systolic bruit over an upper abdominal mass, was shown at exploratory laparotomy to have partial obstruction of the abdominal aorta by a large, overriding tumor nodule which extended posteriorly from the surface of the liver and produced a palpable thrill over the aorta at the time of surgery. A bruit over the liver area may be so caused, or a venous bruit or hum may occur in face of increased arterial blood flow into the area with subsequent shunting into the dilated venous channels.[3, 4] This was particularly well demonstrated in case 14, which demonstrated a loud bruit and marked thrill over the upper abdomen just to the right of the xiphoid process. At laparotomy, numerous massive venous collateral channels were present in this area.

Fever and Hepatoma: Nodular and diffuse intrahepatic extension of the tumor usually occurs by centrifugal growth, with consequent compression of parenchyma, reduction of the blood supply and, finally, necrosis of the nodule.[3, 4] Such necrosis may present a clinical picture of abscess of the liver or fever of unknown origin. In contrast to the virulent course of such patients as described by Berman, case 5 followed a pattern of exacerbations and remissions, and drainage of the liver abscess failed to prevent the eventual deterioration. Fever as a part of the more advanced stages of hepatoma has been frequently stressed, and in one series of 72 cases was present to some extent in 41 patients, most characteristically as an afternoon temperature elevation.[7] Fever as the initial symptom was noted in two cases by Rosenberg and Ochsner,[8] but the presenting clinical picture was not described.

Liver Biopsy: Failure to obtain tissue diagnosis, even with surgical drainage of the abscess cavity on two occasions, in case 5 emphasizes the necessity for adequate, well selected biopsy specimens for examination. Because punch biopsy in trained hands is so easily done, one is apt to rely too heavily on this approach. A comparison of this method in 107 cases of miscellaneous liver disease with 172 similar cases sampled by open surgical biopsy yielded a positive diagnosis in only 40% by punch biopsy and in 98% by the open method.[9] One report lists the successful diagnosis of six hepatomas by needle biopsy,[10] another notes success by needle technic in only two of five hepatoma cases, and 100% success by open surgical biopsy in another seven cases.[7] Needle biopsy is not without risk, since death has followed intraperitoneal hemorrhage from the biopsy site.[9] Most clinicians now feel, however, that in well-trained hands, this is a relatively

safe procedure with a good diagnostic yield, and may be useful in selected patients with suspected hepatoma if surgical exploration is contraindicated.

Diffuse Tumor: Diffuse extension of primary hepatic carcinoma may occur via perisinusoidal spaces or through the sinusoids, occasionally leading to replacement of pre-existing cirrhotic nodules which then appear to consist of tumor cells.[3, 4] That such diffuse involvement may occur rapidly and extensively is well demonstrated by case 6, in which sudden decompensation of liver function occurred (Figure 3). In spite of the nearly complete obliteration of parenchyma by tumor, the thymol turbidity and cephalin flocculation reactions were normal and the alkaline phosphatase activity reached only 25 King-Armstrong units (total serum bilirubin, 30 mg.%). Although it has been stressed that an elevation of the alkaline phosphatase level out of proportion to the degree of jaundice is suggestive of hepatoma,[4, 11] this must be an unusual occurrence. This test was performed in 12 cases in our series and all elevations (in one case to 81 and another to 64 King-Armstrong units) were in association with comparable obstructive jaundice. MacDonald[7] discusses elevation of alkaline phosphatase activity in 14 cases of 21 tested, the average value being 8.9 Bodansky units (highest 29 units), and could show no pattern useful in differential diagnosis. It has been our impression that a marked elevation of serum alkaline phosphatase activity without comparable evidence of obstructive jaundice is more often encountered in metastatic neoplasm of the liver.

Portal Vein Involvement: Early in the course of intrahepatic growth, the tumor cells appear to penetrate the walls of the portal venous tree with subsequent retrograde extension of the tumor and eventual portal vein thrombosis. One careful analysis of cases records some degree of portal vein invasion in 28 of 33 hepatoma cases studied.[12] Extension to the pancreas by this mode of growth has been reported,[4] indicating the manner in which an intrahepatic growth pattern accomplishes extrahepatic organ involvement. In our series, tumor extension to the area of the porta hepatis and the gastrohepatic ligament gave rise to another clinical syndrome, that of intraperitoneal hemorrhage pre-terminally in cases 1 and 2, as well as terminally in one other case.

Hemorrhage with Hepatomas: Massive intraperitoneal hemorrhage is unlikely to be considered due to hepatoma, but four of our patients (cases 1, 2, 3, 12) exhibited such features and it was the presenting complaint in three. Apart from abdominal injury or rupture of an aortic aneurysm, spontaneous intraperitoneal hemorrhage is rare in the male, and excluding gynecological problems, is equally uncommon in the female. Spontaneous rupture of the spleen may occur in malaria or in infectious mononucleosis, and there have been a few reported cases of bleeding from a ruptured gangrenous gall-bladder. In the tropics, hemorrhage may follow rupture of an amoebic abscess.[13] Major textbooks of medicine and liver diseases[14–17] only mention acute intraperitoneal hemorrhage in hepatoma,

but Berman reported 26 cases from the literature prior to 1947 and added six cases of his own. Recent literature [7, 18-20] records at least 12 other such cases and Strong [21] has seen an unknown number of similar cases. While it is stated that intraperitoneal hemorrhage usually originates from rupture of a subcapsular necrotic tumor mass or (rarely) from intraperitoneal rupture of esophageal varices,[3, 8] invasion of the vessels in the gastrohepatic ligament was the source of three bleeding episodes in our series. Melena and hematemesis from esophageal varices or concomitant peptic ulcer have been frequently reported, and the incidence of melena from all causes in this series was 45%. Case 1 was especially interesting by virtue of the presence of hematobilia of a sufficient quantity to produce prolonged and repeated melena and marked bloody distention of the gallbladder. The source of hematobilia through the right hepatic duct from vessels eroded by a tumor mass that had invaded the duct was well demonstrated at necropsy. Seven cases (15%) were noted to have unexplained melena early in the course of the disease without post-mortem evidence of varices, ulcer, or erosion of the intestinal tract to explain the melena. Unexplained melena may be another early clue to the presence of hepatoma.

Distant Metastases: Extrahepatic spread of the tumor is frequent, with metastases evident in from 50 to 73% of autopsied cases. Extrahepatic dissemination occurred in 78% of our cases as proved by necropsy, but more striking were six cases presenting early signs and symptoms from metastases before there was clinical evidence of liver involvement. Lymphatic spread to the periportal and peripancreatic nodes and extensive lymphogenous dispersion is common, varying from 30% to 67% in reported series.[3, 7, 8, 21] Twenty-six cases, or 55% of this group, had node metastases, most often in the regional nodes. Although it has been suggested that lymphatic spread is more frequent in cholangiocellular hepatomas,[22] our experience was too small to allow an evaluation of this statement. The detection of a Virchow's node in case 4, which presented with an almost classic picture of acute cholecystitis and no other findings of neoplasia, led to the correct diagnosis and emphasizes the diagnostic clues that may be gleaned from a careful physical examination. That metastasis may occur prior to evidence of liver derangement is well documented, the most outstanding example to date being a patient with bony metastases detected nine and one-half years prior to death and seven and one-half years before any hint as to involvement of the liver.[23] The duration of symptoms in this patient appears unique, the longest course in our series being 14 months and the average duration being eight and one-half months.

Investigation of the pulmonary vasculature has shown evidence of tumor present in as high as 87% of cases with metastases.[3] This high rate of pulmonary involvement appears related to the early invasion of the hepatic vein radicles with spread via the inferior vena cava and right auricle, and with numerous implants in these three vascular spaces in

case 10 as well as in one other case reported.[7] MacDonald [7] notes involvement of the heart in three cases by growth along the inferior vena cava and into the right auricle, with tumor growth into the right ventricle in one instance. The unusual implantation of a tumor nodule on the cordae tendinae of the tricuspid valve has been observed.[24] Berman's monograph records the finding of involvement of the heart in 12 cases, including one case from his series. To our knowledge, symptoms from involvement of the heart have not been reported. Once the chest cavity is invaded via the pulmonary arterial system, tumor growth may lead to malignant pleural effusion, destruction of parenchyma of the lung or chest wall, or invasion of the systemic circulation by erosion of the pulmonary venous system with widespread hematogenous distribution. In case 8, early invasion of the chest led to respiratory symptoms progressing from cough and dyspnea to a draining fistula and subsequent empyema over a 10-month period, all prior to any hint of hepatic disease. Although attempts at tissue diagnosis were unsuccessful, surgical advances in pleural biopsy technics may now allow accurate diagnosis in cases such as our numbers 8, 9, 10, and 11, with presenting complaints arising from malignant pleural effusion, for these metastatic cells usually retain morphologic characteristics sufficient to allow identification.[3, 4] Since the lungs are a prime site of hematogenous metastases and invasion of the chest cavity may follow lymphatic dissemination as well as direct extension through the diaphragm,[3, 17] hepatoma should also be suspected in cases of lung invasion by tumor even though the primary site is not evident. Following erosion into the pulmonary venous bed, systemic dispersion of tumor cells occurs, with implantation sites ranging from the cranial bones to the femur [3] or any tissue between these sites. Bone is not uncommonly invaded and case 12, as well as two previous reports,[5, 26] demonstrate that a large tumor mass can occur in the clavicle at an early stage of the disease, making simple biopsy diagnosis readily available. The presence of intravascular tumor emboli in glomerular tufts and adrenal gland vessels in case 2, as well as the wide range and high frequency of tumor spread in our series (Table 1), emphasizes the diagnostic opportunities as well as the dilemmas inherent in hepatoma.

Cirrhosis, Infectious Hepatitis, and Hepatoma: The literature abounds with data correlating cirrhosis with hepatoma and, as stated earlier, it is claimed that the most frequent clinical pattern is that of hepatoma complicating the course of known cirrhosis, usually in an alcoholic patient. This relation was true in 11 of our 47 cases; six had previously been jaundiced. It was of interest that of the remaining 36 patients, only five gave a past history of signs or symptoms of liver failure significant enough to produce illness. Table 3 summarizes several reports of the association of cirrhosis and hepatoma: a relation to an initial hepatic injury, whether in the form of viral hepatitis or malnutrition and alcoholism, is suggested but as yet remains to be clearly defined by pathologic studies.

TABLE 3

Summary of reports in the Literature Showing the Relation Between Hepatoma and Cirrhosis of All Types

Author	No. of Hepatoma Cases	Hepatomas with Laennec's Cirrhosis	Hepatomas with Post-necrotic Cirrhosis	Hepatomas with other Cirrhosis	Per Cent Hepatomas with Cirrhosis
Rosenberg and Ochsner[8]	55	0	0	0	71*
MacDonald and Mallory[1]	31	31	0	0	100
Blatchford[27]	16	3	4	0	44
Edmondson and Steiner[28]	78	2	53	8	81
Sanford[18]	38	0	0	0	53*
Steiner and Davies[29]	140	25	77	3	75
Strong et al.[21]	41	0	0	0	83*
Warvi[30]	36	0	0	0	44*
Webb[31]	12	0	0	0	100*
Berman[3]					
Review of literature (1901–1947)	893	0	0	0	67*
Personal cases	75	0	0	0	100*
Total Hepatoma Cases	1,405	Average Per Cent with Cirrhosis			74

* Per cent with cirrhosis but of unspecified type.

Several recent reports indicate a changing incidence rate of hepatoma in the United States and suggest that alteration in the structure of the liver following hepatitis may be an associated factor. In 1951, Berman's summary of the world literature showed the autopsy incidence of hepatoma in the United States to be 0.27%. MacDonald[32] in studying the periods 1917–1946 and 1947–1954, found that the autopsy incidence of hepatoma was 0.34% in the first period, and 0.72% in the latter period, a greater than 100% increase in his Boston experience. Recently MacDonald and Mallory

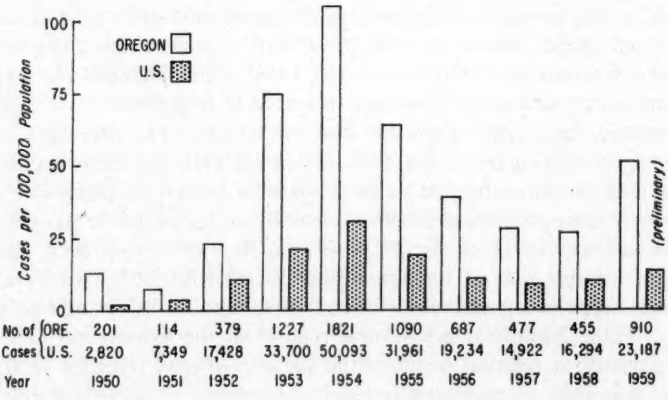

FIG. 4.

reported that postnecrotic cirrhosis following viral hepatitis was complicated by primary liver cancer in 14% of 221 cases. From Russia[33] come two reports of primary liver cancer developing in infants of mothers infected with viral hepatitis during pregnancy, a relationship heretofore not clearly established. The implications of this are beyond the scope of this paper. These reports of an increasing incidence of hepatoma in the United States and a possible association with viral hepatitis are further amplified by Gall's statement[2] "that the type of cirrhosis called Laennec's, fatty, nutritional or alcoholic, is rarely associated with hepatoma. Hepatoma, on the other hand, is a fairly frequent complication of trabecular or septal cirrhosis, which I refer to as posthepatitic cirrhosis. It is particularly common in postnecrotic cirrhosis." These factors have raised the suspicion of a possibly increasing frequency of hepatoma and are based upon the morbidity rate figures of infectious hepatitis supplied by the United States Public Health Service and the Oregon State Board of Health which are plotted in Figure 4. These data demonstrate a disturbingly high peak for the period 1953 to 1955 and may indicate the beginning of another high incidence period that could reveal a cyclic pattern.

If a relationship does indeed exist between viral hepatitis and postnecrotic and posthepatic cirrhosis, as many publications presently bear witness, and the suggestions from the above studies are borne out, it is possible that we can expect an increasing incidence of hepatoma in the near future.

Summary and Conclusions

1. Forty-seven cases of primary carcinoma of the liver were reviewed and 14 patients (30%) were found who presented clinical pictures dominated by what have heretofore been considered atypical and rare features.

2. Nine cases with protean and polymorphic atypical clinical courses were discussed in detail to emphasize the puzzling picture that may confront the clinician dealing with a case of primary liver cancer.

3. A discussion of the signs and symptoms based upon the intrahepatic growth patterns and extrahepatic dissemination of this tumor is offered to aid the clinician in a systematic pathophysiologic approach to diagnosis of the bizarre features of the tumor.

4. It is emphasized that the general notion that cirrhosis and hepatoma are frequently associated is true.

5. Evidence of a possible increase in frequency of hepatoma in the United States and a changing concept of the association of posthepatic cirrhosis and postnecrotic cirrhosis are considered.

6. The occurrence of infectious hepatitis morbidity is presented, and the alarming increase in frequency of this disease and possibly expected increase in one of its complications (hepatomas have developed in 14% of 221 postnecrotic cirrhotics) is emphasized.

ACKNOWLEDGMENT

The authors are indebted for access to the records and pathologic specimens of the following hospitals: University of Oregon Medical School Hospitals and Clinics, United States Veterans Hospital, St. Vincent's Hospital, and Good Samaritan Hospital, all of Portland, Oregon.

SUMMARIO IN INTERLINGUA

Quaranta-septe casos de primari carcinoma del hepate esseva revistate. Esseva trovate que 14 del patientes (30%) presentava tableaus clinic dominate per aspectos que, in le passato, esseva considerate como atypic e rar. Novem casos con cursos clinic de character atypic protee e polymorphe es discutite in detalio pro sublinear le facto que le clinico se trova frequentemente, in casos de primari cancere hepatic, confrontate con tableaus mystificante.

Un discussion del signos e symptomas, basate super le intrahepatic configuration crescential e le extrahepatic dissemination del tumor, es offerite pro assister le clinico in le disveloppamento de un systematic methodologia pathophysiologic pro le diagnose del aspectos bizarre del tumor. Es re-sublineate le facto que cirrhosis e hepatoma es frequentemente associate.

Es considerate observationes que pare indicar le possibilitate de un crescente incidentia de hepatoma in le Statos Unite. Cambiamentos in le currente conception del association de cirrhosis posthepatic con cirrhosis postnecrotic es etiam discutite.

Es presentate le occurrentia de morbiditate in hepatitis infectiose. Es sublineate le alarmante augmento del incidentia de iste morbo e etiam le augmento que es possibilemente a expectar in le incidentia de un de su complicationes. Es notate in iste connexion que hepatomas se ha disveloppate in 14 pro cento de un serie de 221 casos de cirrhosis postnecrotic.

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DIVERTICULOSIS OF THE JEJUNUM WITH MACROCYTIC ANEMIA AND STEATORRHEA *

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Jejunal diverticulosis complicated by macrocytic anemia and steatorrhea has been rarely reported, and the syndrome has remained relatively unknown to the medical profession. Prompt recognition of the syndrome is important, however, if early treatment and beneficial results are to follow. In a review of the literature on jejunal diverticulosis, 15 cases with the triad,[1-12] eight with macrocytic anemia,[11-17] and three with steatorrhea [5, 18, 19] were found. Seven of these patients had studies of absorption of radioactive vitamin B_{12},[5, 7, 12, 16] although none had investigations of absorption of radioactive fat. Only two patients had partial jejunectomies.[9, 12]

This paper will review the syndrome and report the experience with three patients with jejunal diverticulosis. The results of studies with radioactive vitamin B_{12} and of those with radioactive fat, and the effect of partial jejunectomy including the principal area of disease in one patient are included.

Methods

Radioactive vitamin B_{12} absorption was done by the Schilling [20] method, in which 0.5 μg. radioactive vitamin B_{12} is given orally, followed in two hours by a flushing dose of 1,000 μg. vitamin B_{12} parenterally. The 24-hour urinary excretion is collected and assayed for radioactivity. Normal persons excrete over 8%.

Radioactive fat absorption [21] is obtained by the oral administration of an emulsified mixture of I^{131}-labeled triolein in peanut oil, and determination of plasma radioactivity at appropriate hourly intervals. Normal patients have a mean peak plasma I^{131} of 13.7% with a standard deviation of 2.6%. If fat absorption is low, a second radioactive fat meal with addition of 3 gm. pancreatin (Viokase) will result in markedly increased plasma I^{131} levels in pancreatic disease, but essentially unchanged values in intestinal malabsorption.

Case Reports

Case 1. A 64-year-old Negro male was first admitted to the hospital in 1949 with a 20-year history of epigastric fullness after meals, and intermittent bouts of

* Received for publication September 19, 1960.

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vomiting of greenish-yellow bitter fluid postprandially for one year. The hemoglobin was 10.3 gm./100 ml. Diagnoses of jejunal diverticulosis, asthma, and hypertensive cardiovascular disease were made.

In 1950 the patient complained of numbness of the fingers and toes. He was seen elsewhere and signs of subacute combined degeneration of the spinal cord were noted.[16] The red blood cell count was 2,320,000 per cubic millimeter; hematocrit, 25.9%; hemoglobin, 8.4 gm./100 ml.; mean corpuscular volume, 112 cubic microns; mean corpuscular hemoglobin, 36 micromicrograms; and the mean corpuscular hemoglobin concentration, 32%. The bone marrow contained many megaloblasts. Free hydrochloric acid was present in the gastric secretion. Fecal excretion of vitamin B_{12}-Co^{60} decreased after oral antibiotic therapy. Subsequently, the patient was treated successfully with vitamin B_{12} at intervals of six weeks.

The patient was readmitted in 1955. A scout roentgenogram of the abdomen in the erect position, on October 25, showed fluid levels in the left upper quadrant,

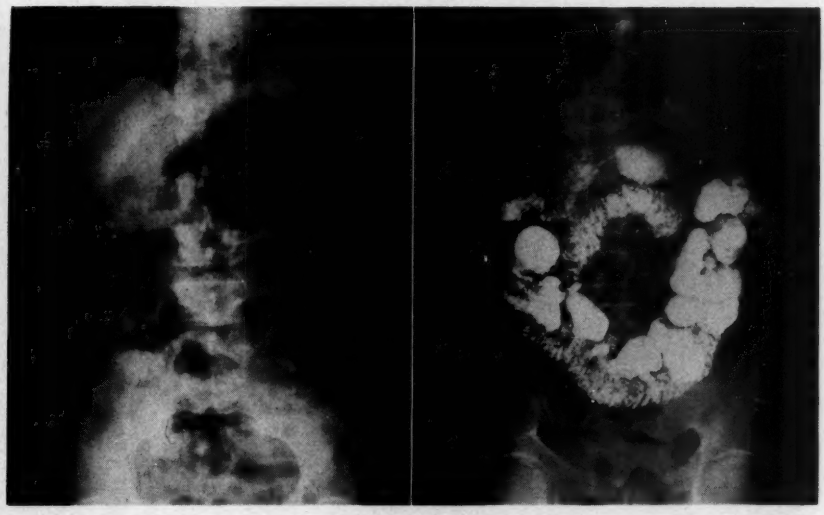

FIG. 1 (left). Scout roentgenogram of the abdomen in the erect position in case 1.
FIG. 2 (right). Gastrointestinal roentgenogram before operation in case 1.

probably in the jejunal diverticula (Figure 1). In a Schilling test with vitamin B_{12}-Co^{60} on October 26, 7.1% of the material was excreted in the urine in 24 hours.

In 1957 the patient returned to the hospital with flatulence, belching, anorexia, and a loss of 15 pounds in weight. The serum albumin was 2.4 gm./100 ml., and the globulin 4.8 gm. The absorption of radioactive fat was borderline low with a peak of 10.1% plasma I^{131}. On February 27 a large number of the jejunal diverticula were noted on the gastrointestinal series (Figure 2). An excision of 160 cm. of jejunum was performed on May 20 (Figure 3). The specimen contained 65 diverticula, many in pairs, along the mesenteric border. These varied from 1.5 to 6.5 cm. in diameter. Examination of the microscopic sections revealed that the mucosa was normal, the submucosa was infiltrated with many round cells, and the muscularis was markedly attenuated with separation of the layers (Figures 4, 5). On June 12 the Schilling test was repeated and 25% urinary excretion in 24 hours

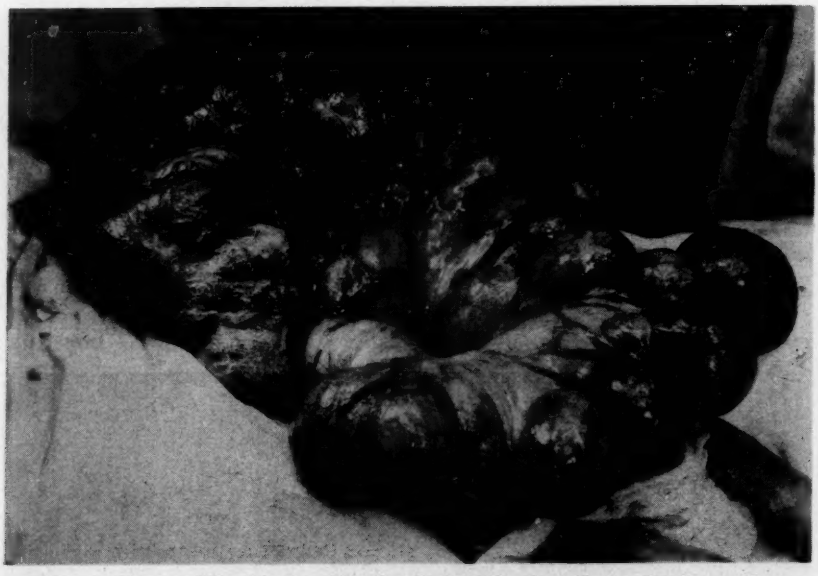

FIG. 3. A part of the jejunum with diverticula at the time of operation in case 1.

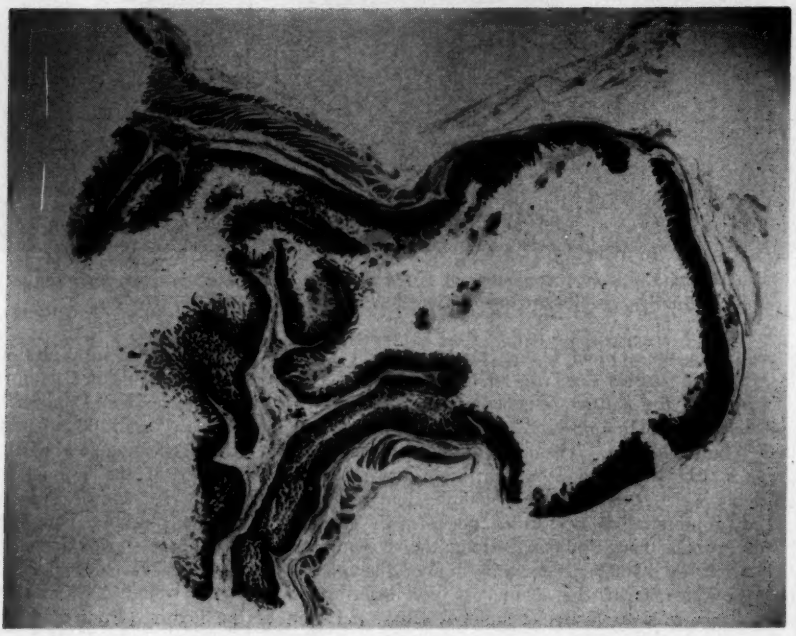

FIG. 4. Photomicrograph of diverticulum of jejunum in case 1 (× 5).

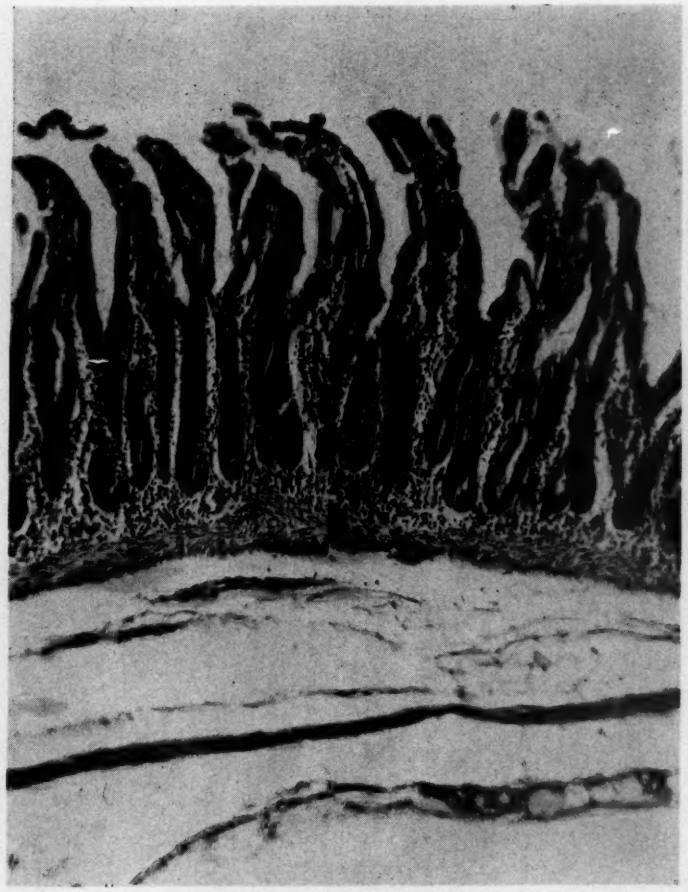

FIG. 5. Photomicrograph of diverticulum of jejunum in case 1 (× 100).

was found. Another gastrointestinal series showed only one or two remaining diverticula (Figure 6).

The hemoglobin was maintained for the next six months without the administration of vitamin B_{12} and the patient regained 15 pounds. He died on December 27, 1958, from hypertensive cardiovascular disease complicated by uremia. At the postmortem examination, left ventricular hypertrophy and multiple diverticula of the small and large bowel, 1 to 2 cm. in diameter, were found.

Case 2. A 75-year-old white female was first seen at this hospital in 1952 because of weakness, pallor, marked diarrhea, and a loss of 70 pounds in weight. The red blood cell count was 1,480,000 per cubic millimeter; hemoglobin, 4.7 gm./100 ml.; hematocrit, 15%; mean corpuscular volume, 111 cubic microns; mean corpuscular hemoglobin, 32 micromicrograms, and the mean corpuscular hemoglobin concentration, 29%. The serum albumin was 2 gm./100 ml., and the globulin, 2.8 gm. Free

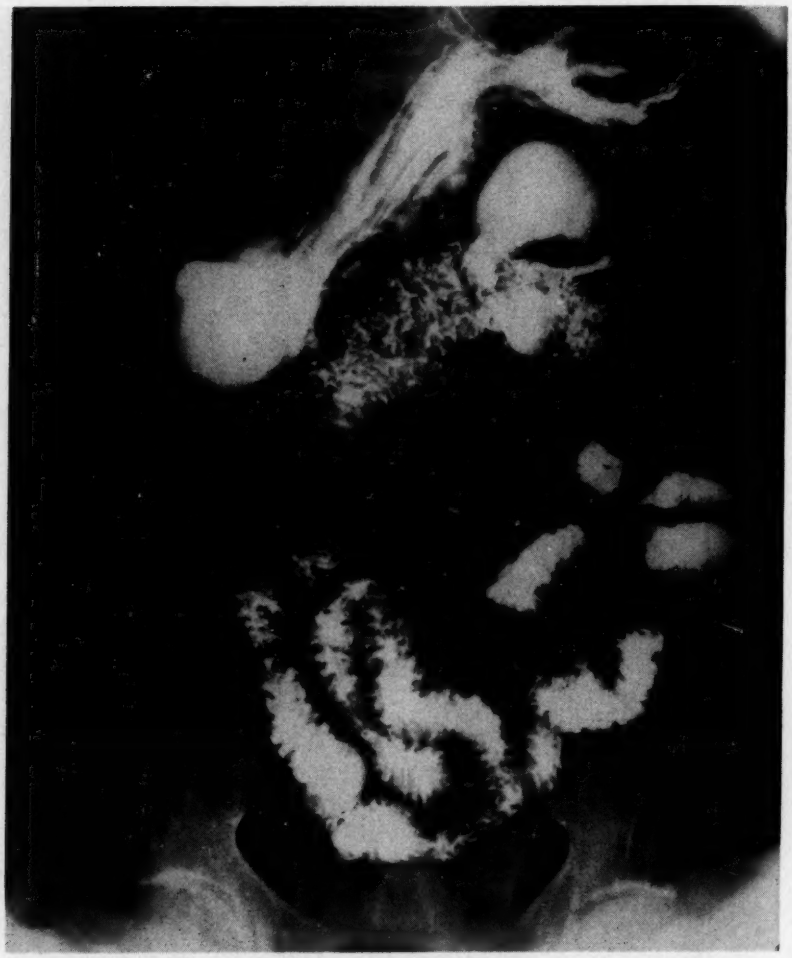

FIG. 6. Gastrointestinal roentgenogram after operation in case 1.

hydrochloric acid was present in the gastric secretion. A roentgenogram of the abdomen in the erect position on August 11 showed many fluid levels in the small bowel. Numerous large diverticula of the small intestine were seen on the gastrointestinal roentgenogram. Hypoplasia of the erythroid series was found in the bone marrow. The hematologic response to liver extract was good with a 15% reticulocytosis in five days.

The patient stopped her medication and was readmitted in 1957 for similar complaints and a thrombophlebitis of the left leg. On January 22, 1958, 1.9% of a dose of vitamin B_{12}-Co^{60} was excreted in the urine in 24 hours. Following six days of treatment with chloramphenicol and sulfathalidine, in a similar test 9.7% was excreted. A peak plasma I^{131} of 7.4% was reached when an I^{131} fat absorption

study was done, which was not improved by the administration of pancreatin. The patient failed to respond to treatment. She died on April 11. The post-mortem examination showed numerous jejunal diverticula, 4 to 5 cm. in diameter, with hyperemia and edema in areas, and some large diverticula of the transverse, descending, and sigmoid colon. Death was due to bilateral pulmonary emboli from thrombophlebitis of the left lower extremity.

Case 3. A 76-year-old white male was hospitalized elsewhere in 1952 for weakness, syncopal episodes, and a loss of 15 pounds in weight. The red blood cell count was 3,090,000 per cubic millimeter; hemoglobin, 9.7 gm./100 ml.; hematocrit, 30%; mean corpuscular volume, 98 cubic microns; mean corpuscular hemoglobin, 32 micromicrograms; and mean corpuscular hemoglobin concentration, 31%. The serum albumin was 2.2 gm./100 ml., and the globulin 3.4 gm. Free hydrochloric acid was not present in the gastric juice even after the administration of histamine. The bone marrow contained many megaloblasts. The gastrointestinal series showed multiple jejunal diverticula. Treatment with vitamin B_{12} produced a reticulocytosis of only 3% and the hematologic remission during the following months was slow.

He was admitted to this hospital in 1954 for cardiac failure, a history of severe diarrhea, and loss of 12 pounds in weight of two months' duration. The red blood cell indices were normal. The barium enema roentgenogram showed a normal colon

TABLE 1

Peak Plasma I^{131} Levels (in % of dose) after I^{131}-Labeled Fat Meals, Without and With Pancreatin

Case	Without Pancreatin	With Pancreatin
1	10.1%	—
2	7.4%	7.1%
3	5.6%	6.9%

but an ileus of the small intestine. The gastrointestinal series demonstrated massive jejunal diverticula.

In January, 1958 the patient was readmitted because of diarrhea. He was emaciated and confused. The serum albumin was 1.6 gm./100 ml. and the globulin 3.6 gm. The result of the gastric analysis and the small bowel series confirmed the previous findings. Urinary excretion of vitamin B_{12}-Co^{60} was 0.4% in 24 hours. After five days of treatment with tetracycline, the excretion of another dose was 5.8%. A peak plasma I^{131} of 5.6% was obtained when a study of absorption of I^{131}-labeled fat was done and little change occurred after the administration of pancreatin. Temporary cessation of the diarrhea followed a course of tetracycline and cortisone. He subsequently left the hospital. The patient died on April 11, 1958.

COMMENTS

Our three patients with jejunal diverticulosis all had low vitamin B_{12}-Co^{60} absorption, poor I^{131}-labeled fat absorption (Table 1), hypoalbuminemia, and evidence of stasis of gastrointestinal contents. The first two cases showed chronic inflammation of the diverticula on histologic examination. Radioactive vitamin B_{12} absorption became normal in the first patient after surgical excision of the diverticula, and was improved in the last two after broad spectrum antibiotic therapy (Table 2).

Partial jejunectomy for diverticula with studies of vitamin B_{12} absorption has been reported in two other cases. The first patient excreted 10%

TABLE 2

Effect of Antibiotics or Surgery on Urinary Excretion of Vitamin B_{12}-Co^{60}

Cases	Before Therapy	After Antibiotics	After Surgery
1	7.1%	—	25%
2	1.9%	9.7%	—
3	0.4%	5.8%	—

of vitamin B_{12}-Co^{60} in the urine before and 1% after operation,[12] indicating a poor result. Surgery in the second patient was successful. He had a low serum level of 128 micromicrograms of vitamin B_{12} per ml. before and a normal level of 288 micromicrograms per ml. after the operation.[9] The third patient, the one in the present series, excreted 7.1% of radioactive vitamin B_{12} in the urine before and 25% after the operation. The response in this patient was particularly gratifying and indicated excellent absorption of the radioactive material.

Macrocytic anemia usually responds to the administration of vitamin B_{12} and broad spectrum antibiotics, and steatorrhea with concomitant diarrhea to the latter. If a response is not obtained operation should be considered for patients in good general physical condition.

Of all 18 cases reported, including the present three, at least 10 demonstrated stagnation of the intestinal stream. Nine had symptoms of anemia as the earlier manifestation and the other nine had evidence of steatorrhea. In addition, at least nine had low serum albumin, and four had low serum calcium. Chronic inflammation in the diverticula has also been previously noted.[2, 13]

Apparently stagnation in the diverticula, with bacterial overgrowth and inflammatory changes, is responsible for the multiple defects in absorption. Bacterial interference with vitamin B_{12} absorption is evident from the improvement following antibiotic therapy, as noted in our two cases (Table 2), as well as in four others from the literature (Table 3)[7, 12, 16] The mechanism of bacterial interference could be due to irritation and inflammation of the intestinal wall, or to competition for vitamin B_{12} between the bacteria and the

TABLE 3

Effect of Tetracycline Drugs on Fecal or Urinary Excretion of Vitamin B_{12}-Co^{60}

Cases	Before Antibiotics		After Antibiotics	
	Fecal Excretion	Urinary Excretion	Fecal Excretion	Urinary Excretion
1. Krevans et al.[16]	88.5%*	—	46.7%*	—
2. Gellman[7]	High*	—	Normal*	—
3. Scudamore et al.[12]	—	0%	—	13%
4. Scudamore et al.[12]	—	1%	—	11%

* Normal fecal excretion is below 50%.

host. However, the lowered fat absorption, hypoalbuminemia, and hypocalcemia are better explained by bacterial inflammatory changes or irritative food breakdown products rather than by bacterial requirements for the nutriments.

If, as postulated, stasis in the diverticula is the primary cause of the ensuing absorptive difficulties, some help in understanding the mechanism might be obtained from experimental studies with production of a blind loop in animals. Such interference with the normal peristalsis of the gastrointestinal tract would parallel the changes seen in patients with jejunal diverticula. A study of the blind-loop syndrome in dogs was performed by Tonnis and Brusis.[22] An anemia, usually hyperchromic, occurred in two to four months. This was corrected by excision of the sac and the administration of intestinal antiseptics or liver extract. When antiperistaltic loops were formed in the small intestine of rats by Cameron et al.,[23] a macrocytic anemia followed in one to five months in half of those animals in which the loops were in the upper two-thirds of the small intestine. The rats were cured by the administration of folic acid and liver extract. The authors concluded that the anemia was caused by stagnation of the intestinal contents and a change in bacterial flora.

Summary

Three additional cases of jejunal diverticulosis with macrocytic anemia and steatorrhea are reported. Frequently, other absorptive deficiencies are also present. The administration of one of the broad spectrum antibiotics improves vitamin B_{12} absorption and may alleviate the symptoms of diverticulitis. Vitamin B_{12} may be used effectively as substitution therapy. Surgical excision of the diverticula was effective in correcting the absorptive deficiencies.

Summario in Interlingua

Diverticulosis jejunal, complicate per anemia macrocytic e steatorrhea, se trova reportate rarmente, e le syndrome ha remanite relativemente incognoscite al profession medical. Tamen, le prompte recognition del syndrome es importante si un precoce therapia con resultatos benefic es desirate. Esseva trovate in un revista del litteratura de diverticulosis jejunal 15 casos exhibiente le triade, octo con anemia macrocytic, e tres con steatorrhea. In septe de iste casos, studios del absorption de radioactive vitamina B_{12} esseva disponibile, sed investigationes del absorption de grassia radioactive non habeva essite effectuate in ulle. Jejunectomias habeva essite executate in solmente duo del patientes.

Le presente communication constitue un revista del syndrome e un reporto del experientias in le casos de tres patientes con diverticulosis jejunal. Omnes habeva basse valores pro le absorption de vitamina B_{12} a Co^{60}, un paupere absorption de grassia marcate con I^{131}, hypoalbuminemia, e indicationes de stase del contento gastrointestinal. Le prime duo del tres casos monstrava un inflammation chronic del diverticulos in un examine histologic. Le absorption de radioactive vitamina B_{12} deveniva normal in le prime patiente post excision chirurgic del diverticulos. In le

altere duo, ille absorption esseva meliorate post therapia con antibioticos a large spectro.

Le mechanismo de malabsorption in iste entitate simula apparentemente illo trovate in le syndrome a ansa cec. Stase in le diverticulos e excessos de crescentia bacterial con inflammation chronic resulta. Multiple defectos de absorption—incluse illo de vitamina B_{12}, grassia, albumina, e calcium—es producite. Le defective absorption pote esser le effecto de un inflammation del pariete del jejuno o de un concurrentia pro vitamina B_{12} inter le bacterios e le hospite. Le resultatos le plus commun es anemia macrocytic e steatorrhea.

Clinicamente, le anemia responde al administration de vitamina B_{12}, e le steatorrhea e le concomitante diarrhea responde al administration de un del antibioticos a large spectro. Quando nulle responsa es obtenite, un intervention chirurgic debe esser considerate in le caso de patientes in bon condition physic.

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IDIOPATHIC HYPERLIPEMIA AND ISCHEMIC HEART DISEASE * †

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Idiopathic hyperlipemia is an inborn error of lipid metabolism characterized by elevated levels of serum triglyceride, cholesterol, and phospholipid. The elevated serum triglyceride level in this disorder imparts a milky appearance to the serum even in the fasting state and differentiates it from the closely allied familial disorder, idiopathic hypercholesterolemia. Patients with idiopathic hyperlipemia frequently exhibit xanthomatous deposits in skin and tendons. They are prone to develop attacks of acute pancreatitis, mild diabetes is common, and the liver and spleen may be enlarged. While the condition was initially regarded as benign, this view is no longer tenable following recognition that it is associated with a remarkably high incidence of myocardial infarction.[1] Boggs et al.[2] have attributed a death to myocardial infarction in a 10-year-old child with this disorder and the same authors have concluded, from their study of the genetic mechanisms involved, that idiopathic hyperlipemia is transmitted as an autosomal recessive. In the series of cases reported by Adlersberg,[1] 34% of new cases exhibited evidence of ischemic heart disease. Three of four patients studied in this department were found to have ischemic heart disease.

Numerous reports have indicated that ischemic heart disease is associated with abnormalities in serum lipids in the absence of familial hyperlipemia. This observation has led to the conjecture that abnormal degrees of lipemia may be directly involved in the pathogenesis of myocardial infarction. While it has long been known that elevated cholesterol levels are associated with and may precede clinical manifestations of ischemic heart disease, it is recognized that serum triglycerides are also elevated in this disease.[3] Hyperlipemia per se may be harmful. It is claimed to increase blood coagulability,[4] to decrease fibrinolysis,[5] to cause clumping of red blood cells,[6] to impair tissue oxygen uptake,[7] and to reduce myocardial blood flow.[8]

The reason for the elevated lipids in patients with idiopathic hyperlipemia has not been identified. The increased lipemia following fat ingestion and its reduction by fasting have suggested, however, that defective removal of ingested triglyceride is involved in this disorder. A similar phenomenon appears to exist in ischemic heart disease. Thannhauser and

* Received for publication July 11, 1960.
Presented at the Forty-first Annual Session of The American College of Physicians, San Francisco, California, April 4–8, 1960.
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Stanley [9] have shown that after ingestion of I^{131}-labeled triolein by patients with idiopathic hyperlipemia, an excessive amount of this labeled fat is retained in the blood stream. Likoff et al.[10] and Seller et al.[11] have shown excessive and prolonged alimentary lipemia in patients with ischemic heart disease, using the same technic.

Because of the particularly close association of idiopathic hyperlipemia and myocardial infarction, it was decided to study some aspects of triglyceride metabolism in this disorder, and to see in what way it may be related to that present in patients with myocardial infarction without evidence of familial lipemia.

Materials and Methods

Three groups were studied. Group 1 comprised four male patients with idiopathic hyperlipemia, on whom brief histories are presented.

Patient J. T. This 30-year-old physical training instructor complained of abdominal discomfort. The only abnormal finding on examination was

Table 1

Fasting Plasma Lipid Levels in Four Patients with Idiopathic Hyperlipemia on Initial Determination

Patient	T.E.F.A., mEq./L.	Triglyceride, mEq./L.	Cholesterol, mg.%	Phospholipid, mg.%
J.T.	93.4	71.0	512	586
M.E.	68.2	45.5	449	620
I.L.	120.0	99.3	495	547
F.A.	39.2	18.3	590	449
Mean & Std. Dev.	80.2 ± 34.6	58.5 ± 34.7	511.5 ± 58.7	550.5 ± 74.0

an enlarged spleen palpable two inches below the left costal margin. A fasting blood sample was noted to be grossly lipemic and yielded the lipid values shown in Table 1. All known secondary causes for this lipemia were excluded by appropriate tests of hepatic, renal, and endocrine function. Treatment with a 20 gm. fat diet daily resulted in a decrease in serum lipids but the patient complained of fatigue and weakness on this diet. He was, therefore, allowed two additional 50 gm. fat meals per week and an attempt was made to reduce further his serum lipid levels by systemic administration of heparin. One hundred milligrams were given twice daily by subcutaneous injection. Three days later plasma total esterified fatty acid levels had fallen from 42 to 28.2 mEq./L. On this day he experienced an episode of classical anginal pain at rest and a previously normal electrocardiogram showed changes of acute myocardial ischemia. Later that day he complained of abdominal pain and fullness. On examination, the liver and spleen were palpable at the umbilicus. Heparin was stopped. The electrocardiogram became normal the following day and the liver and spleen decreased in size

over the next three weeks. He subsequently remained well and symptom free on a low fat diet.

Patient M. E. A 52-year-old white male physician presented with a Bell's palsy. Blood drawn at this time was lipemic and a fasting blood specimen on the following morning remained lipemic. Plasma lipid values are shown in Table 1. No cause could be found to explain his lipemia. Clinical, x-ray, and electrocardiographic studies failed to reveal any other abnormality. There was a history of xanthomatosis in the patient's mother and of diabetes mellitus, myocardial infarction, and psoriasis in three siblings, all of whom had elevated lipid levels. He was treated with a diet in which 25% of the calories were derived from fat, and has remained well and symptom free.

Patient I. L. This was a 63-year-old white male university professor whose serum was submitted for a cholesterol determination. It was grossly lipemic. Several fasting samples subsequently obtained were all lipemic. He gave a history of mild diabetes since 1944 and had sustained a myocardial infarct in 1958. His diabetes was well controlled with 14 units of protamine zinc insulin daily, and he had never been ketotic. Fasting blood sugar levels were normal and no glycosuria was detected on any of his visits. It was concluded that his lipemia could not be attributed to the diabetes mellitus and no other cause for lipemia could be discovered. Marked reduction in plasma lipid levels was attained with a fat restricted diet. He has remained well and symptom free.

Patient F. A. This 58-year-old white garage attendant had sustained a myocardial infarct in 1943 and another in 1944. He had recovered and had led an active life until 1957, since which time he had experienced severe angina pectoris. For several months he had experienced pain and stiffness of the hands and fingers. On examination his fingers were stiff and swollen and xanthomatous deposits were palpable in the palmar tendons. Tuberous xanthomata were present over both elbows and eruptive xanthomata were present on the knees and buttocks. The heart was enlarged, the blood pressure 205/100 mm. Hg. The electrocardiogram revealed an old anterior infarction. A fasting blood sample was lipemic and plasma lipid levels were as shown in Table 1. No known cause for this lipemia could be discovered. Reduction in plasma lipids and considerable clinical improvement were achieved with a low fat diet.

Group 2 comprised 15 men aged 43 to 64 who had sustained myocardial infarcts three to six months prior to the study. None of these patients were diabetics, and they were free of hepatic and renal disease. Group 3 included 15 healthy middle-aged men aged 36 to 63. The mean age of these two groups was not significantly different.

In all three groups a fat tolerance test was carried out by feeding one-half pint of heavy cream after an overnight fast and withdrawing blood while fasting and at three, five, seven, nine, and 24 hours after fat ingestion. In six

of the healthy men and in all other subjects 100 μc of emulsified I^{131}-labeled triolein were mixed with the cream immediately prior to ingestion. Plasma total esterified fatty acid content of all blood samples was measured by the method of Stern and Shapiro.[12] In two patients with idiopathic hyperlipemia and in all other subjects plasma cholesterol [13] and phospholipid [14] were measured in the fasting, in the five-hour, and in the nine-hour samples. Plasma triglyceride levels in the fasting samples were calculated by subtracting fatty acids of cholesterol and phospholipids from total esterified fatty acids.[15] The radioactive lipid present in the plasma was measured and expressed as lipid-bound I^{131} by counting a 2 ml. aliquot of plasma in a deep-well scintillation counter, using the method of Beres et al.[16] Blood volume was calculated as 7.7% of the body weight in kilograms [17] and plasma volume was obtained from this value after determination of the hematocrit. In patient M. E. the fat tolerance test was repeated two weeks after the initial test, but with the addition of intravenous heparin, 50 mg., at zero, three, five, and seven hours after fat ingestion. In this patient and in patient J. T. the test was repeated 12 months and 17 months, respectively, after their commencing a fat restricted diet.

The significance of the radioactive measurements listed in the following section requires some explanation of their nature and derivation. I^{131}-labeled triolein is an oil in which 99% or more of the I^{131} is bound to the double bond of oleic acid. After absorption, breakdown of this labeled fatty acid results in the liberation of the bound I^{131}. Thus, total I^{131} activity in blood after absorption is the sum of radioactivity in two main fractions, lipid bound I^{131} and free I^{131}. It follows that if no breakdown or utilization of I^{131}-labeled fatty acid occurs after absorption, total radioactivity will be synonymous with lipid bound radioactivity and the ratio $\frac{\text{lipid bound } I^{131}}{\text{total } I^{131}}$ will be unity. When fatty acid utilization occurs normally, however, this ratio will be less than one, and the actual figure will give some indication of the extent to which the labeled fatty acid has been broken down. Because the free I^{131} liberated is excreted in the urine, the level of urinary I^{131} may also be an index of fatty acid catabolism. Twenty-four hour urinary I^{131} levels were, therefore, measured in all three groups.

Results

Values for plasma lipids in the four patients with idiopathic hyperlipemia on their initial visit are shown in Table 1. All plasma lipid levels were elevated, with the greatest increase above normal being in the triglyceride fraction. In Table 2 the mean lipid values in these four patients are compared with the mean values in 15 patients with ischemic heart disease and in 15 healthy men. Following ingestion of the labeled fat by the patients with idiopathic hyperlipemia, three experienced a progressive rise in plasma total esterified fatty acid and in lipid bound I^{131} levels until nine hours after fat

TABLE 2

Mean Fasting Plasma Lipid Levels in Health, in Ischemic Heart Disease, and in Idiopathic Hyperlipemia

	T.E.F.A., mEq./L.	Triglyceride, mEq./L.	Cholesterol, mg.%	Phospholipid, mg.%
15 Healthy	14.2 ± 3.0	3.4 ± 2.2	222 ± 38	280 ± 64
15 I. H. D.	19.0 ± 3.5	5.5 ± 2.9	316 ± 74	344 ± 56
4 I. H. L.	80.2 ± 34.6	58.5 ± 34.7	511 ± 58	550 ± 74
P Value I. H. D. Healthy	<0.01	<0.01	<0.01	<0.02
P Value I. H. D. I. H. L.	<0.01	<0.01	<0.01	<0.01

ingestion. In the fourth patient, I.L., these levels started to fall sometime between five and seven hours after ingestion but were still abnormally high at nine hours (Figure 1). In Table 3 mean fasting and postprandial total esterified fatty acid levels in the three groups are shown. These levels were significantly higher than normal at all times in persons with ischemic heart disease. In healthy subjects, an absolute increase in total esterified fatty acid of 6.5 mEq./L. occurred five hours after fat ingestion. Two hours later this level was 4 mEq./L. above fasting and at nine hours was 0.4 mEq./L. above fasting. In ischemic heart disease the absolute increase in total esterified fatty acid at five hours was 10.4 mEq./L. At seven hours, however, little change had occurred in this level and at nine hours the level exceeded the fasting value by 5.8 mEq./L. In idiopathic hyperlipemia, total esterified fatty acid levels were significantly higher than normal at all times and exceeded the fasting level by 17.1 mEq./L. at nine hours.

Lipid bound I^{131} levels in the three groups are shown in Table 4. These levels were measured at five, nine, and 24 hours only in the healthy group. While lipid bound I^{131} was higher than normal at all times in ischemic heart disease, this value was significantly abnormal at nine hours only. In idiopathic hyperlipemia, levels were also higher than normal at all times but

TABLE 3

Comparison of Mean Plasma T.E.F.A. Levels (mEq./L.) Following Fat Ingestion in Health, in Ischemic Heart Disease, and in Idiopathic Hyperlipemia

	Fasting	3 hours	5 hours	7 hours	9 hours
15 Healthy	14.2 ± 3.0	17.6 ± 4.2	20.7 ± 6.3	18.2 ± 4.9	13.8 ± 3.9
15 I. H. D.	19.0 ± 3.6	25.1 ± 4.1	29.4 ± 7.9	29.4 ± 8.0	24.8 ± 7.3
4 I. H. L.	35.3 ± 5.2	37.8 ± 6.9	45.4 ± 5.6	47.5 ± 7.2	52.4 ± 12.7
P Value Healthy I. H. D.	<0.01	<0.01	<0.01	<0.01	<0.01
P Value I. H. D. I. H. L.	<0.01	<0.01	<0.01	<0.01	<0.01

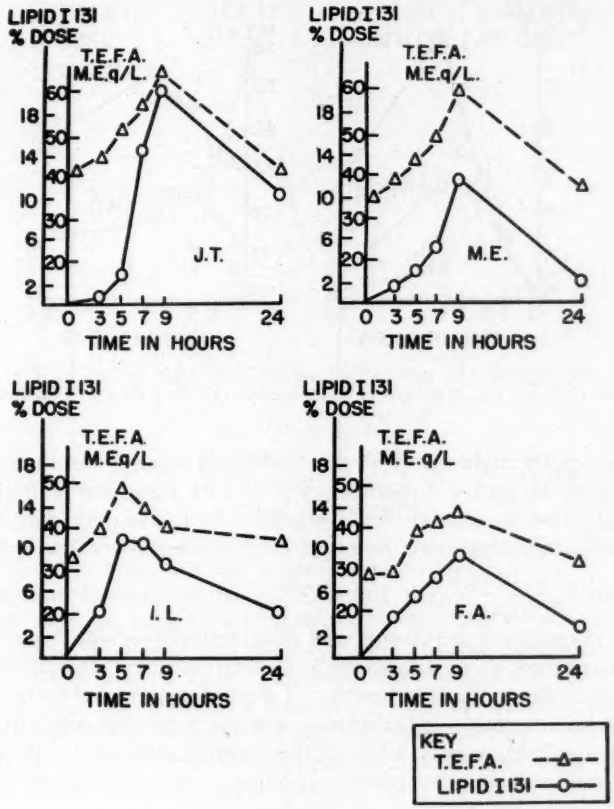

FIG. 1. Postprandial plasma lipid levels in four patients with idiopathic hyperlipemia.

TABLE 4

Comparison of Mean Plasma Lipid I^{131} Levels (% Ingested Dose) in Health, in Ischemic Heart Disease, and in Idiopathic Hyperlipemia Following Ingestion of I^{131}-Labeled Triolein

	3 hours	5 hours	7 hours	9 hours	24 hours
6 Healthy	—	4.5 ± 2.9	—	1.6 ± 0.3	0.2 ± 0.1
15 I. H. D.	3.4 ± 1.2	6.0 ± 2.8	6.9 ± 2.7	5.3 ± 2.2	0.5 ± 0.3
4 I. H. L.	2.4 ± 1.8	5.4 ± 3.9	9.4 ± 4.8	12.6 ± 5.5	4.8 ± 3.9
P Value Healthy / I. H. D.	—	<0.10	—	<0.01	<0.02
P Value I. H. D. / I. H. L.	<0.10	<0.50	<0.10	<0.01	<0.01

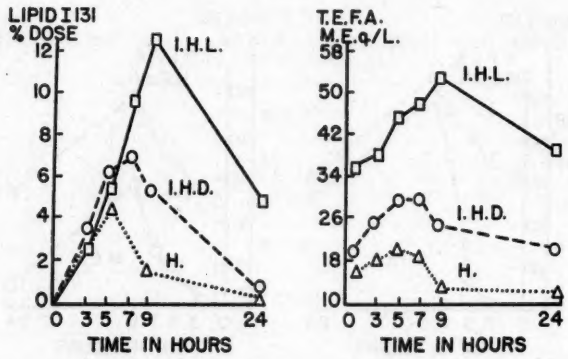

FIG. 2. A comparison of postprandial plasma lipid levels in health (H), in ischemic heart disease (I.H.D.) and in idiopathic hyperlipemia (I.H.L.) after ingestion of I^{131}-labeled fat.

were significantly higher only at nine and at 24 hours. At these times the patients with idiopathic hyperlipemia also had significantly higher levels than those found in ischemic heart disease. In the healthy individuals, the plasma radioactive lipid never exceeded 50% of the total radioactivity present at any time (i.e., $\frac{\text{lipid } I^{131}}{\text{total } I^{131}} \times 100 < 50\%$) but it exceeded this value at the outset in idiopathic hyperlipemia and progressively increased with time, so that at nine hours it constituted 60% of total plasma radioactivity as compared with a value of 25% in health. Twenty-four hours after fat ingestion, patients with idiopathic hyperlipemia retained a grossly abnormal amount of radioactive lipid, namely 4.8% of the ingested dose, and this represented 51% of total radioactivity present in plasma at this time, as compared with

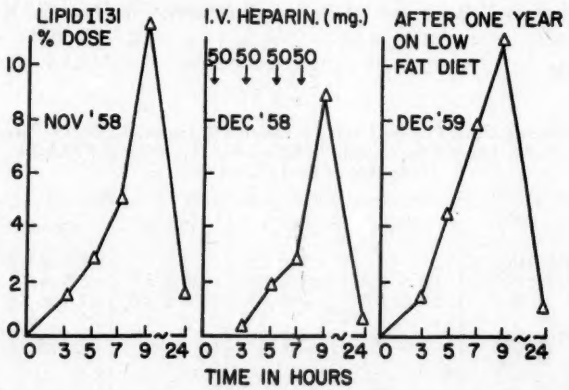

FIG. 3. Patient M.E. Postprandial plasma lipid levels after ingestion of I^{131}-labeled fat on three occasions.

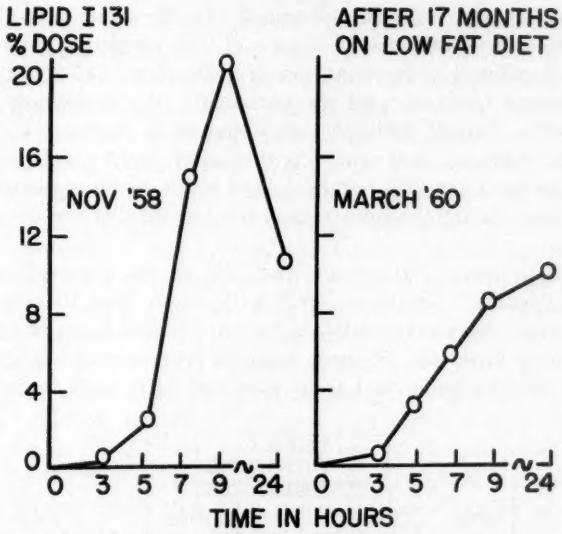

FIG. 4. Patient J.T. Postprandial plasma lipid levels after ingestion of I^{131}-labeled fat, before and after treatment with low-fat diet.

the normal value of 10%. A comparison of changes in radioactive lipid with changes in total esterified fatty acid in the three groups is shown in Figure 2. These indices tended to parallel each other and suggested that the radioactive fat was handled in a manner similar to the natural fat.

In patient M.E. the fat tolerance test was repeated two weeks later with systemic heparin administration and again 12 months later without heparin, after plasma lipid levels had been reduced by a low-fat diet (Figure 3). Normal lipid bound I^{131} levels were present at three, five, and seven hours during heparin administration but at nine hours a highly abnormal amount of radioactive fat was present. The amount of lipid I^{131} remaining at 24 hours during heparin administration was 0.48% which, although lower

TABLE 5

Changes in Plasma Lipids on Low-Fat Diet in Four Patients with Idiopathic Hyperlipemia

Patient	Triglyceride (mEq./L.)		Cholesterol (mg.%)		Duration of Diet in Months
	Before Diet	After Diet	Before Diet	After Diet	
J.T.	71.0	11.4	512	115	45
M.E.	45.5	12.5	449	290	51
I.L.	99.3	6.3	495	332	3
F.A.	18.3	11.5	590	400	1
Mean & Std. Dev.	58.5 ± 34.7	10.4 ± 2.8	511 ± 58	284 ± 121	

than without heparin, was still abnormal. In the third test, although the fasting triglyceride level was 12.5 mEq./L. as compared with the initial value of 45.5 mEq./L., the ingestion of radioactive fat again resulted in abnormal lipemia and indicated the persistence of the previously observed clearing defect. Similar findings were apparent in patient J.T. (Figure 4) when the fat tolerance test was repeated after dietary restriction for 17 months. The most recently obtained lipid levels in the patients with idiopathic hyperlipemia after various times on a low-fat diet are shown in Table 5.

The 24-hour urine I^{131} content was 32% of the ingested dose in idiopathic hyperlipemia. This was significantly lower than the values of 45% in ischemic heart disease and 50% in health. These latter two values were not significantly different. Figure 5 shows postprandial changes in serum cholesterol, phospholipids, and total esterified fatty acid in health and in

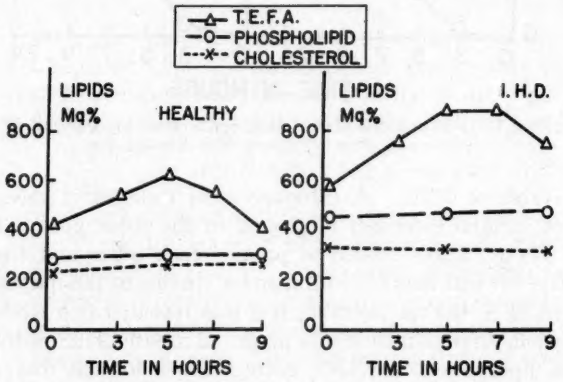

FIG. 5. Changes in plasma lipid levels in health and in ischemic heart disease (I.H.D.) after fatty meal.

ischemic heart disease. These findings indicated that elevation of cholesterol and phospholipids after fat ingestion contributed very little to the rise in total esterified fatty acid and that this increase was, therefore, attributable to increase in the triglyceride fraction.

DISCUSSION

The characteristic chemical abnormality in idiopathic hyperlipemia is gross elevation of fasting serum triglyceride level in the absence of any known cause. The association of this chemical defect with certain clinical features, such as ischemic heart disease, diabetes mellitus, xanthomatosis, and hepatosplenomegaly, together with a family history of similar disorders, helps establish the diagnosis. The mechanism for the elevated triglyceride levels in this disorder has not been established. In the four patients studied

the progressive elevation of postprandial plasma total esterified fatty acid and radioactive lipid levels, well above those found in health, and the continued elevation at nine hours, when fasting levels should be attained, suggested that removal of ingested triglyceride was impaired. An alternative explanation for the abnormally high radioactive lipid level was that dilution of the radioactive fat had occurred in a greater than normal fat pool. To support this finding, it has been shown that the half-life of intravenously administered labeled triglyceride is directly related to the amount of triglyceride administered.[18] In two of the patients with idiopathic hyperlipemia, however, in whom the plasma lipid pool was reduced by dietary fat restriction, the repeat fat tolerance test revealed the same degree of radioactive fat retention at 24 hours as occurred in the initial test. The finding that only 32% of the ingested radioactivity had appeared in the 24-hour urine of these four patients, as compared with 50% in health, suggested that delayed removal of ingested triglyceride was accompanied by or even responsible for delayed breakdown of its fatty acid component. In healthy animals, the reverse situation would appear to hold true, as Micheljik and Bragdon [19] have shown that when serum C^{14}-labeled triglyceride removal is accelerated by intravenous heparin, increased catabolism of fatty acid occurs, as evidenced by increased $C^{14}O_2$ production. Postprandial lipid levels in patients with ischemic heart disease indicated that these patients also removed ingested fat more slowly than normal.

Despite the clinical and familial differences between the two abnormal groups in this study, their similar lipid abnormalities suggested that the mechanism underlying the defective lipid metabolism may have been one and the same in both and that any difference between the two conditions was really one of degree. While idiopathic hyperlipemia is known to be a genetically determined defect, emphasis has also been placed on the family history in patients with ischemic heart disease. A familial incidence of ischemic heart disease was found in 50% of Cassidy's 100 cases [20] and was four times as common in the 744 young cases of Yater et al.[21] as in normal controls. While idiopathic hyperlipemia has been considered a relatively uncommon disorder, a recent large scale survey [22] in Sweden indicated that 3% of a college student population of 1,000 was considered to be suffering from this disorder. The importance of triglyceride metabolism in ischemic heart disease is now receiving increased attention. It has recently been shown that lower triglyceride levels are found in South African Bantu than in South African Europeans and it is known that the former race has a considerably lower incidence of ischemic heart disease than the latter.[23] Albrink and Man [3] have emphasized in their studies that abnormalities in serum triglycerides were more commonly found in this disorder than were abnormalities in serum cholesterol levels. It seems quite likely that if serum triglyceride levels are measured as extensively as are cholesterol levels at present, patients will be found who will fall between the two groups de-

scribed in this study. The decision to label these as cases of idiopathic hyperlipemia or ischemic heart disease with unusual glyceridemia will be purely arbitrary. In the series reported by Albrink and Man,[3] for example, two patients had serum triglyceride levels which exceeded those found in patient F.A. in this study.

The possibility that familial idiopathic hyperlipemia and ischemic heart disease with defective lipid metabolism represent different grades of the same disorder must, however, remain speculation until the exact mechanism for the abnormality is established. It now seems that more than one defect may be operating in familial lipemia, for Hirschorn et al.[24] and Havel and Gordon[25] have reported that some cases exhibit lipemia clearing after heparin injection and others, who appear unable to produce lipoprotein lipase, do not.

While there is no absolute proof that the abnormal lipemia that exists in these conditions is directly involved in the pathogenesis of ischemic heart disease, it would appear that if the presence of lipemia is potentially harmful, then these patients are more exposed to such potentially harmful effects. In any patient, therefore, who exhibits impaired removal of ingested triglyceride, restriction of dietary fat would seem a rational and desirable means of obtaining and maintaining normal lipid levels. This therapy may be supplemented by accelerating fat removal with various clearing agents, of which heparin has been the most widely used. The development of orally effective heparin or of other long-acting clearing agents may prove of value in these disorders. These drugs should be used with some caution, however, as the sudden clearing of large amounts of triglyceride from plasma may produce undesirable and even harmful effects. It has been shown that in health most of the triglyceride removed from plasma is normally deposited unchanged in the liver[26] and that breakdown to glycerol and fatty acid occurs in this organ. When spontaneous episodes of abdominal pain have occurred in patients with idiopathic hyperlipemia, liver and spleen enlargement has been described, and in at least two instances[27, 28] liver biopsy has revealed this organ to contain fat. Other investigators[29-31] have suggested that the sudden onset of abdominal pain is due to sudden infiltration of the liver with fat and consequent stretching of its capsule. While the sudden enlargement of the liver and spleen reported in patient J.T. following heparin administration may have been coincidental, it is thus quite possible that the triglyceride cleared from plasma in this patient was deposited in these organs as a result of the heparin administration. There are indications that heparin may induce what may be called "rebound lipemia." Following heparin administration three, five, and seven hours after fat ingestion by five healthy medical students[32] lipemia clearing was accelerated. Twenty-four hours later, however, serum lipid levels in these subjects rose above fasting level and in one individual, lipemia of the order observed in idiopathic hyperlipemia was present at 24 hours. A similar "rebound lipemia" has been described by

Tietz et al.,[33] who showed that a decrease in total esterified fatty acid levels three hours after heparin administration was followed at six hours by an increase above pre-heparin levels. If heparin is used as a clearing agent in lipemia, it would seem advisable first to attain maximal reduction of serum lipid levels by dietary means.

Summary and Conclusion

Four patients with idiopathic hyperlipemia were studied. Fasting serum in these patients exhibited the characteristic elevation of the serum triglyceride level together with elevation of phospholipid and cholesterol. Ingestion of a fatty meal containing I^{131}-labeled triolein by these subjects produced excessive and prolonged lipemia. Similar, but less marked, fasting and postprandial lipid abnormalities were also observed in 15 patients with previous myocardial infarction, who had none of the clinical features associated with the familial disorder. While heparin administration during the repeat of a fat tolerance test in one patient resulted in lower radioactive lipid levels, the test remained abnormal. In this patient and in one other, a repeat of the fat tolerance test 12 and 18 months later, at a time when significant reduction in serum lipid levels had occurred following dietary fat restriction, indicated that the initial abnormality had persisted. A reduction in serum lipid levels occurred in all four patients when dietary fat was restricted.

It is concluded that ischemic heart disease is extremely common in idiopathic hyperlipemia, a disorder in which disturbed lipid metabolism is readily apparent and well recognized. The use of a fat tolerance test indicates that a very similar but less readily apparent metabolic disturbance in lipid metabolism also exists in most cases of ischemic heart disease. These findings add support to the concept that abnormal lipid metabolism may be directly involved in the pathogenesis of myocardial infarction.

Acknowledgments

I am indebted to Doctors Richard T. Beebe and Thomas F. Frawley for permission to report details of their patient F.A., and to Doctor Joseph T. Doyle for his criticism and help in the preparation of the manuscript.

Summario in Interlingua

Hyperlipemia idiopathic es un innate error del metabolismo lipidic, characterisate clinicamente per un altissime incidentia de infarcimento myocardial e chimicamente per marcate elevationes del nivellos seral de triglycerido in stato jejun. In recente tempores il ha devenite apparente que mesmo in le absentia de iste disordine familial, patientes con ischemic morbo cardiac exhibi elevate nivellos de triglycerido, a parte le communmente recognoscite hypercholesterolemia de illes.

Iste similitudes stimulava un studio del metabolismo triglyceridic in quatro patientes con hyperlipemia idiopathic, 15 patientes con previe occurrentias de infarcimento myocardial, e 15 normal subjectos de controlo de etates correspondente.

Post jejunation transnocturne, cata subjecto recipeva como bibita un medie pinta de crema spisse, continente grassia marcate per I^{131}. Specimens de sanguine esseva

obtenite a intervallos in le curso del sequente 24 horas, e le nivellos lipidic in illos esseva mesurate. Le quatro patientes con hyperlipemia idiopathic exhibiva multo marcate e anormalmente prolongate lipemia postprandial. Simile sed minus marcate anormalitates esseva observate in le patientes con ischemic morbo cardiac. Le uso de grassia radioactive revelava que 24 horas post le ingestion, le patientes con ischemic morbo cardiac reteneva 0,5 pro cento e subjectos normal 0,2 pro cento del dose ingerite.

Le constatationes indicava que omne le morbide subjectos in iste studio esseva incapace de eliminar le ingerite triglycerido ab le sero con un rapiditate normal. Insimul con le observation facite per alteros que lipemia augmenta le coagulabilitate, interfere in le acceptation de oxygeno per le tissus, e reduce le fluxo de sanguine myocardial, le presente constatationes presta supporto al conception que un anormalitate del metabolismo triglyceridic es forsan directemente interessate in le pathogenese de infarcimento myocardial. Le constatationes etiam supporta le recommendation de restringer le ingestion dietari de triglycerido como mesura de possibile utilitate therapeutic e prophylactic in casos de ischemic morbo cardiac.

Post que un considerabile reduction del nivellos seral de triglycerido esseva effectuate per medio de un dieta a basse contento de grassia in patientes con hyperlipemia idiopathic, un repetition del test de tolerantia pro grassia in duo de illes revelava que le elimination de ingerite triglycerido remaneva grossiermente defective. In duo subjectos le clearance non esseva substantialmente meliorate per le administration de heparina, ben que il habeva essite demonstrate que iste droga produce un alte concentration de lipase de lipoproteina in le subjectos examinate.

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OBESITY IN MEN: A CLINICAL STUDY OF TWENTY-FIVE CASES * †

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Current clinical concepts of obesity have been derived almost entirely from the study of obese women. By chance or by design most obese groups which have been studied have contained few if any men, and little attention has been paid to the possibility that obesity in men may differ from obesity in women. The present clinical study of 25 obese men done at the Hospital of the University of Pennsylvania indicates that a difference does exist. Its most striking finding, however, is a fortuitous one which may well apply also to obese women: there are striking differences between men who became obese as children and those who became obese as adults.

Methods

Twenty of the subjects were referred from the medical outpatient department over a period of nine months, and five from the psychiatric clinic over a period of 12 months. Each subject was told that he was going to be examined by a group of doctors interested in his overweight, and that he would be given help to lose weight, if he should desire it, after the examinations were completed.

The only prerequisite for inclusion in this study was that the patient be at least 30% overweight as determined by standard height and weight tables. Median overweight was 64%, with a range from 32% to 115%. Median age was 38, with a range from 18 to 70. All subjects were either of lower or lower middle class backgrounds; 12 were white and 13 were Negro.

The study of each subject included a detailed medical and psychiatric history, physical examination, psychologic tests, and, where indicated, home visits by a social worker. Psychologic tests consisted of the following: California Psychological Inventory, Taylor Anxiety Scale, Leary Adjective Check List, Rorschach Test, Thematic Apperception Test, Draw a Figure Test, and the Wechsler-Bellevue Adult Intelligence Scale. These tests were administered and scored independently of the psychiatric examination. Physical activity of 17 of the 25 subjects was measured for a two-week

* Received for publication October 11, 1960.
† Supported in part by Research Grant M-3684 from the National Institute of Mental Health, National Institutes of Health, U. S. Public Health Service.
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period by means of New Haven Clock Company pedometers. Twelve subjects were seen for one or two hours of psychotherapy every week or two for periods up to two years, and four were treated for shorter periods of time. Nine subjects did not accept treatment.

"Juvenile Obesity"

The most striking and unexpected finding of this study was the marked difference between persons who became obese as children and those who became obese as adults. Clinicians have long recognized important physiologic and psychologic differences between so-called "juvenile diabetes" and "adult diabetes." Differences fully as striking were found in this study between what may be called by analogy "juvenile obese" and "adult obese" men.

Incidence: The incidence of obese adults who were obese as children has been variously reported [1, 2] as 19% and 32%. In this study 11 of 25 subjects (44%) were "juvenile obese."

Severity: Juvenile obese subjects are reported to show a greater per cent of overweight than do the adult obese.[2] The juvenile subjects in the present study showed a greater maximal per cent of overweight, although the difference was not statistically significant. Median per cent overweight of the juvenile subjects was 76 (range 44 to 105), whereas the median of the adult obese was 52 (range 33 to 115).

Weight Fluctuations: Bruch [3] has stated that "changes and fluctuations in weight are a much better index of the severity of the weight problem than [is] the percentage of weight excess." Accordingly, we made an attempt to classify the lifelong weight histories of our subjects into stable and unstable patterns. The former category included prolonged successful weight reduction without undue effort, and stable weight histories without attempts to reduce. The unstable category contained "saw-tooth" weight patterns in which repeated successful attempts at weight reduction were followed by gains in weight, as well as by repeated, unsuccessful attempts at weight reduction.

Tables 1 and 2 present the lifelong weight histories of 24 subjects. Juvenile obese subjects reported unstable patterns far more frequently than did adult obese persons, the Fisher Exact Probability Test revealing a difference significant at the 1% level.

Intelligence Quotient: The median intelligence quotient of the juvenile obese subjects, as measured by the Wechsler-Bellevue Intelligence Scale, was 122 as compared with 100 for the adult obese subjects, a difference which is significant at the 5% level. Values for the individual subjects are listed in Table 1.

Negative Findings: No difference between juvenile obese and adult obese subjects was found in four regards: physical activity, psychiatric diagnoses, eating patterns, and consumption of alcohol.

TABLE 1

"Juvenile Obesity" Pattern

Number	Age	Weight Pattern	I.Q.	Eating Pattern	Maximal Per Cent Overweight	Psychiatric Diagnosis
1	22	Unstable	133		95	Passive-aggressive personality, passive-aggressive type
2	26	Unstable	110		105	Depressive reaction in passive-dependent personality
3	45	Unstable	139	Night-eating	72	Paranoid personality
4	18	Unstable	95		105	Stable
5	28	Unstable	89	Night-eating	62	Chronic undifferentiated schizophrenic reaction
6	26	Unstable	131		61	Passive-aggressive personality, passive-aggressive type
7	36	Unstable	146	Binge-eating	80	Cyclothymic personality
8	22	Unstable	132	Binge-eating	81	Passive-aggressive personality, passive-dependent type
9	38	—	120		—	Passive-aggressive personality, passive-dependent type
10	18	Stable	82		61	Passive-aggressive personality, passive-dependent type
11	65	Stable	122		44	Schizoid personality
Median and range	26 (18–65)		122 (82–146)		76 (44–105)	

Psychologic Functioning: The unique difficulties of the juvenile obese men were most dramatically manifested in their psychologic functioning. In contrast to the adult obese subjects, they tended to show a greater degree of anxiety, disturbances in their self-concepts, impaired perception of others' view of them, and severe difficulty in relating to women.

Self-concept: The obesity of six of the 11 juvenile obese subjects colored their concepts of themselves and their bodies in a most derogatory manner. Such derogatory self-concepts were found in none of the 14 adult obese subjects.

TABLE 2

"Adult Obesity" Pattern

Number	Age	Weight Pattern	I.Q.	Eating Pattern	Maximal Per Cent Overweight	Psychiatric Diagnosis
12	48	Unstable	89		68	Stable
13	45	Unstable	144		46	Stable
14	35	Unstable	131		49	Stable
15	45	Stable	102		36	Schizoid personality
16	50	Stable	106		46	Stable
17	35	Stable	105		33	Schizoid personality
18	45	Stable	96	Night-eating	34	Stable
19	40	Stable	98		66	Chronic anxiety reaction
20	70	Stable	84		44	Chronic brain syndrome
21	45	Stable	94		56	Chronic alcoholism
22	40	Stable	82		77	Emotionally unstable personality
23	58	Stable	94		115	Passive-aggressive personality, passive-dependent type
24	36	Stable	111	Night-eating	92	Passive-aggressive personality, passive-dependent type, with alcoholism
25	36	Stable	105		84	Emotionally unstable personality
Median and range	45 (35–70)		100 (82–144)		52 (33–115)	

A juvenile obese subject said, "Just looking at myself in the store window makes me feel terrible. It's gotten so I'm very careful never to look by accident. It's a feeling that people are right to hate me and to hate anyone that looks as fat as me. As soon as I see myself I feel an uncontrollable burst of hatred. I just look at myself and say, 'I hate you, you are loathsome.' "

Contrast the more casual reaction of an adult obese man to a similar stimulus: "You know I caught a glimpse of myself in the mirror this morning and I was surprised at how fat I had become. It made me feel it's time for me to get some of this weight off."

Misperception by Others: The same six juvenile obese subjects showed striking misperceptions of how others viewed them. At times these misperceptions had a delusional quality but the delusion rarely if ever spread beyond the area of overweight. Such misperceptions were not reported by any of the adult obese group.

One juvenile obese man said, "My overweight makes me withdraw from people. I think that they look down on me. They laugh at me even though I try to tell myself they don't mean anything by it."

Another reported, "Weight was always a problem. If I missed a note in my music class and someone said, 'you always mess it up, man,' then I would think maybe it's because of my weight."

By contrast the adult obese subjects rarely commented on how others regarded them. When asked specifically, one obese man reported, "The cosmetic point of view bothers me only indirectly—through my wife. She objects to it; I think she thinks a lot about it."

Relationships with Women: The hypersensitivity of the juvenile obese subjects to how others regarded them was most marked in their relationships with women. For example, only three of the 11 juvenile subjects were married at the time of the study, compared with 12 of the 14 adult obese subjects. They readily expressed their concerns about their inadequacy with women.

One young man stated, "I don't see myself as a suitable sexual object. . . . If I were a girl, I wouldn't want me for sex." Another remarked, "I was kind of bashful as far as meeting young ladies. I always thought they preferred tall slender people and I didn't like to be insulted."

By contrast, an adult obese subject boasted, "Hell, doc. I can get a woman any time I want to. I'm a good looking guy and if you know anything about how women are, you know that I can get one without any trouble."

The juvenile obese men responded to their problems with women in a variety of ways. One subject, until he was in his sixties, kept away from "respectable girls," who, he felt, would reject him, and he confined his sexual interest to prostitutes. Another juvenile obese subject projected his con-

tempt for himself onto women and then developed a paranoid hostility towards them. Two other juvenile obese subjects became overt homosexuals, while another's sexual fantasies were primarily homosexual.

The types of personality problems that have just been described were not present in every instance of juvenile obesity. For two of the juvenile obese subjects in this series overweight had connotations that heightened self-esteem. For them, size meant strength, massiveness, huskiness, and masculinity, and both were football players. The obesity of two other juvenile obese subjects had no apparent effect on their concepts of themselves.

It was striking that in none of the 14 adult obese subjects did their obesity affect their self-esteem or their concept of themselves, nor did it become an important factor in their interpersonal relationships. Some believed that they would feel better physically if they weighed a little less, some were troubled by feelings of mildly injured vanity, and others were nagged about their weight by their wives. Not one adult obese subject, however, expressed unrealistic concern about his weight.

Obese Men and Food Intake

Eating Patterns: Some obese persons consume their food in curious, stereotyped eating patterns. Since these patterns were observed in populations consisting almost entirely of women, we were interested to learn that they also occurred in men (Tables 1, 2).

The "night-eating syndrome" [4] is characterized by morning anorexia, evening hyperphagia, and insomnia, and occurs during periods of life stress. The incidence of this syndrome seems to depend upon the incidence of emotional disturbance in the population under study. For example, it was found in 20 of 25 obese women in a psychosomatic clinic, but in only 14 of 100 obese women in a nutrition clinic. In the present study the night-eating syndrome was observed in four of 25 subjects.

"Eating binges" [5] are characterized by the consumption of enormous amounts of food in relatively short periods of time and are regularly followed by severe discomfort and expressions of self-condemnation. They, too, occur primarily during periods of life stress and there is evidence that obese persons who later develop anorexia nervosa come from this group. Two subjects in this series were binge eaters.

Relationship of Food Intake to Life Stress: It has been frequently reported that overeating in obese persons increases during periods of stress.[3, 6] In a survey of 500 patients Freed [7] reported that 370 ate more when nervous or worried, 95 ate more when idle or bored, and only 35 patients noted no connection between food intake and emotional stress. Such reactions contrast strikingly with those of non-obese individuals who are reported to eat less when upset or depressed.

Eleven of 25 obese men reported that they ate more when upset or depressed. Six subjects, on the other hand, paradoxically stated that they ate

less when under stress. Four subjects did not know whether they ate more or less and four reported that they ate the same when under stress as they did ordinarily.

Curiously, the nature of the stress that led to overeating varied considerably from person to person, and different stresses sometimes led to different patterns even in the same individual. Some subjects distinguished between different kinds of stress and desire for food. For example, one said, "When people nag me I feel bad and blue, but not hungry. But when people accuse me of things I feel bad and hungry."

Isolated individuals reported even more complex relationships between stress and food intake. One, for example, noted that tension accompanying distressing interpersonal relationships led to abdominal sensations which were relieved by eating. Tension resulting from impersonal stresses such as examinations, on the other hand, as well as feelings of loneliness and depression, did not produce these sensations, but did produce a desire to eat.

Food Preferences: Some writers have reported strikingly uniform food preferences in their obese patients. Hecht,[8] for example, noted that 12 of his 13 obese patients preferred high calorie, especially fatty, foods. Richardson [9] felt that fruits were chosen with above average frequency and that obese women preferred candy, sweets, pies, cakes, soft drinks, and milk. Mayer,[10] however, reported no uniformity in food preferences among obese subjects.

The obese men in the present study showed no consistency in their food preferences. One stated that he enjoyed high calorie foods, "bread with lots of butter, milk, salad dressing, Danish pastries." Another stated that he preferred highly spiced and protein foods. Two preferred sweet foods. One emphasized his taste for salad dressing and mustard. Another subject reported, "I usually eat sandwiches and cheap stuff. I get a loaf of bread and a can of lunch meat and eat the whole darn thing. When I'm really depressed, I drink a quart of milk." One man noted a strong preference for peanut butter and jelly sandwiches, while another reported an equally strong preference for steaks.

The two binge eaters reported striking shifts in food preferences when they were upset. One stated that during binges his tastes became "Rabelaisian" and he induged heavily in oysters, steaks, and large amounts of "extravagant foods" in contrast to his usual, plainer fare. The other, who usually preferred meat and vegetables, would turn to fatty and concentrated carbohydrate foods when he was upset.

Alcohol Intake: We found in other studies only casual reference to the role of alcohol consumption in human obesity, and our experience with obese women had led us to believe that it was of little importance. We were therefore surprised to find that alcohol accounted for a significant proportion of the caloric intake of 11 subjects, and that it seemed to increase *food* intake in some.

Two subjects were frank alcoholics. One was periodically incapacitated by his drinking, while the other precariously maintained a job as a bartender. Each reported an alcohol intake of about 2,000 calories per day. Nine other subjects regularly drank considerable amounts of alcohol although none would be considered alcoholic; alcohol did not appear to interfere with their employment or with their family life. Nevertheless, they regularly consumed 300 to 1,200 calories a day in alcoholic beverages, and this consumption was often exceeded during celebrations and periods of stress.

Alcohol sometimes contributed to excessive food intake in an unexpected manner. The outcome of a period of stress was often determined for one subject by the accessibility of alcohol. If none was available he could often fight off his impulse to overeat. If, however, he began to drink, he lost all ability to control his eating and embarked on an eating binge. Such apparent facilitation of food intake by alcohol was noted by other subjects in whom, however, it did not reach such intensity.

Estimation of Food Intake: A report by Beaudoin and Mayer [11] confirms the long-standing clinical impression that the reports of obese women concerning their food intake are inaccurate, in that they consistently underestimate the amount they eat and deny the most obvious relations between their food intake and their body weight. It is not as generally recognized that this underestimation of food intake is frequently accompanied by reports of anorexia. Neither of these phenomena was a feature of obese men. Indeed we were surprised at the freedom with which the obese men reported even enormous food consumption. The hearty appetite which characterizes the old stereotype of the obese person found at least some support in this group. We had reason to believe that food intake was underestimated in only two of the 25 subjects. The obese men rarely reported anorexia, and then it was in such circumstances as during the hangover from a drinking or eating binge.

Other Characteristics of Obese Men

Physical Activity: Several studies [12–15] indicate that decreased physical activity plays a role in human and experimental obesity. One of the authors previously measured the physical activity of 15 obese women by means of mechanical pedometers and found that they walked less than half as far as a matched non-obese control group.[16]

We measured the activity of 17 obese men to determine whether decreased physical activity is as characteristic of obese men as it is of obese women. The activity of these subjects was compared with that of 17 non-obese men matched for age, race, and type of occupation.

The average distance walked by the obese men was 3.7 miles per day as compared with six miles per day for the non-obese men. Comparable figures for the women were two miles per day for obese women and 4.9 miles per day for non-obese women. Comparison of groups by the Wilcoxon

matched-pairs signed-ranks test revealed that the difference between groups was significant at the 5% level for men and at the 1% level for women. Thus, obese men were less active than non-obese men, but this difference was not as striking as that found among women. These findings have been recently reported in greater detail elsewhere.[17]

Emotional Factors: Several authors [18-21] have reported the presence of emotional disturbance and of distinctive and pathologic personality types in obese persons. We therefore carefully evaluated our subjects to ascertain both the extent of their psychopathology and the presence of any distinctive personality patterns.

The impression that a very high per cent of obese persons manifest evidences of emotional disturbance was confirmed in the present series. Intensive psychiatric interviews and psychologic testing revealed that the work and/or family adjustment of 20 of the 25 subjects was significantly impaired by emotional disturbance.

Was this high incidence of emotional disturbance specific to obese persons? To answer this question 18 non-obese men were matched individually for referral source, age, and educational level with 18 of the obese subjects, and were subjected to the same intensive psychologic testing. These tests revealed that the control group had the same high level of emotional disturbance as the obese group, and no tests revealed any psychologic differences between the two groups.[22]

Clinical psychiatric study likewise did not show any distinctive personality type among the obese men. Instead we found a remarkable heterogeneity of personality patterns. This heterogeneity is illustrated in Tables 1 and 2, which list the diverse psychiatric diagnoses of the 20 emotionally disturbed subjects.

Results of Treatment: Four studies [23] suggest that weight reduction programs are more successful with men than with women. The difference in results, however, may be due to nothing more than the different selection processes for men and for women. Presumably only those women come to treatment who have already been unsuccessful in the weight reduction regimens so frequently publicized by women's magazines; the more successful women never consult a doctor about weight problems. Among men, on the other hand, the doctor is frequently the first source of information about weight reduction regimens, and the more successful candidates have not been eliminated prior to treatment.

The present study provides an opportunity to evaluate the results of treatment of 25 men, only two of whom had sought assistance for weight reduction. The results are every bit as unsatisfactory as those reported for women, and suggest that the usual superior weight reduction record of men may well be due to selection of subjects. Only one of our subjects lost more than 20 pounds, six lost between 10 and 20 pounds, nine lost less than 10 pounds, and nine did not accept treatment.

Comment

The most striking finding to emerge from this study is the remarkable difference between men who have been obese all their life and those who became obese when adult, a difference most evident in their psychologic functioning. Many of the "adult obese" subjects had severe personality problems, but in no case did these problems seem influenced by their obesity. For example, not one of 14 adult obese subjects revealed any disturbance in his concept of his body. By contrast, the obesity of six of 11 "juvenile obese" subjects colored their concepts of themselves and their bodies in a most derogatory manner.

This distinction between juvenile and adult obesity has an important therapeutic implication: the physician will encounter far less difficulty in the treatment of adult obese than of juvenile obese patients. Among the former the obesity is a circumscribed area of difficulty, with none of the emotional significance which is so frequently a characteristic of juvenile obese persons. Although weight reduction is difficult for each group, adult obese persons can approach treatment in a realistic way, succeeding or failing on the merits of the case. Juvenile obese persons, on the other hand, particularly those in whom there is a disturbance of body image, all too often undertake weight reduction programs for wildly unrealistic reasons. Although the patient and sometimes the unwary physician may be gratified by a huge initial loss of weight, prolonged efforts are almost doomed to failure, and the history of these patients is one in which weight gain follows weight loss with discouraging regularity. Although the effect of such repeated weight losses and weight gains on the coronary arteries is still unclear, their effects on the morale and self-esteem of the obese person are not. Each failure adds its burden of discouragement and its proof of inadequacy. In this small group of obese persons the physician should exercise great caution in prescribing weight reduction, even for patients who desire it and who protest that only loss of weight will improve their life adjustment. This attitude may be the best evidence that improvement of the life situation is a prerequisite to successful weight reduction.

What are the origins of the psychologic differences between adult obese and juvenile obese men? It appears that age of onset is crucial to one's view of his obesity. The concept of one's self and particularly of one's body seems to be so firmly established by adulthood that it is not easily disturbed by changes in body contours. Before adulthood, however, such concepts appear to be far more fluid and far more readily affected by unfavorable experiences. Our data indicate, furthermore, that it is adolescence which is the period *par excellence* when unfavorable experiences with body weight leave lasting effects upon the body image. Such "critical periods," during which specific influences have decisive effects upon development, have been demonstrated by modern ethology.[24] Erikson[25] has shown that in man adolescence is the decisive period for development of the individual's sense of personal identity. Living through this period with a distinctively dif-

ferent body build which subjects the person to ridicule and abuse appears unusually effective in imprinting a derogatory body image.

Not every juvenile obese man revealed disturbances in the concept of his body. If all of them were subjected to the ridicule and abuse of their peers, how did some escape? It appeared that in families which viewed overweight as a sign of strength and health, the presence of obesity actually heightened self-esteem. This was particularly true of two juvenile obese men who had been football players and who thought of their size in terms of strength and manliness.

Two questions remain unanswered. To what degree are the differences between juvenile obese and adult obese men a result of the higher intelligence quotient of the juvenile obese, and are similar differences present also in women? At the present time we are conducting studies designed to answer these questions. Preliminary results indicate that the differences are not due to differences in intelligence and that women show the same results as men.

A goal of much investigation of "psychosomatic" conditions has been the delineation of personality features specific for each condition. Early reports of such specificity have often not been confirmed by subsequent studies carried out with greater methodologic rigor. Nevertheless the search continues for psychologic features specific for a psychosomatic condition, and by carefully delimiting the population under study, some workers have been able to discover such specific features. Bruch,[26] for example, in her report on the family frame of obese children, was able to discover distinguishing psychologic characteristics of an obese population. Three subsequent studies which also dealt with carefully selected obese populations have reported similar findings.[16, 27, 28] We were accordingly interested in seeing if we could find such specific features in a sample confined to obese men. Our inability to discover any *common* personality features, let alone *specific* ones, emphasizes the heterogeneity of "psychosomatic" conditions in general and obesity in particular.

Summary

Twenty-five obese men admitted to the medical and psychiatric clinics of the Hospital of the University of Pennsylvania were studied by a variety of clinical technics. Marked variability in the behavior of these men was observed, and no common personality type was found which would distinguish them from non-obese men. However, two types of obese men could be distinguished by the age of onset of their obesity. Men who became obese before adulthood were heavier, had more unstable weight histories, and had higher intelligence quotients than did men who became obese as adults. Furthermore, the obesity of these "juvenile obese" subjects frequently colored their concepts of themselves and their bodies in a most derogatory manner, a finding which was not observed in any of the 14 "adult obese" men.

In contrast to the relationship of alcohol intake to obesity in women, this factor played a greater role and physical inactivity a lesser role among these obese men.

SUMMARIO IN INTERLINGUA

Vinti-cinque obese masculos, admittite al clinicas medical e psychiatric del Hospital del Universitate Pennsylvania, esseva studiate per un varietate de technicas clinic pro determinar le etiologia de lor obesitate, le differentias in lor comportamento dietari, e le possibile differentias inter le obesitate de illes como un gruppo integre e le obesitate de feminas como gruppo integre. Un marcate variabilitate del comportamento de iste masculos esseva observate, e nulle commun typo de personalitate esseva notate que haberea polite distinguer les ab masculos non-obese. Tamen, duo typos de masculo obese poteva esser distinguite secundo le etates del declaration del obesitate. Le subjectos in qui le obesitate habeva comenciate ante le attingimento de un etate adulte esseva plus pesante, habeva plus instabile carrieras de peso, e possedeva plus alte coefficientes de intelligentia que le subjectos qui deveniva obese como adultos. In plus, le obesitate del subjectos con "obesitate juvenil" frequentemente colorava le conception que illes habeva de se mesme e de lor corpores in un negativissime maniera. Isto non esseva le caso inter le 14 masculos con "obesitate adulte."

Per contrasto con le relation inter le ingestion de alcohol e le presentia de obesitate in feminas, iste factor habeva un plus importante rolo e inactivitate un rolo minus importante in le caso del masculos obese.

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RENAL GLOMERULAR AND VASCULAR LESIONS IN PREDIABETES AND IN DIABETES MELLITUS: A STUDY BASED ON RENAL BIOPSIES * †

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IT has long been suspected that the vascular disease seen in patients with diabetes mellitus might not be directly related to the control, severity, or duration of the carbohydrate defect.[1-8] If this is true, it modifies and broadens the etiologic concept of diabetes.

Of all forms of vascular disease, those found in the retina and in the kidney are the most specific for diabetes.[9] The literature on the renal glomerular involvement in diabetes is difficult to interpret. The presence or absence of the nodular (Kimmelstiel-Wilson) lesion does not depend on the severity [10] or on the clinical control [7] of the carbohydrate defect. Once the Kimmelstiel-Wilson lesion is present, its progression, and, consequently, the time of appearance of the clinical syndrome, is related to the duration of the known carbohydrate intolerance and to the adequacy of clinical control of this defect.[11] While this is generally true, there are many exceptions, as indicated by Rifkin et al.,[12] and Lambie and Macfarlane,[13] who have commented on the extreme variability of the time of appearance of the nodular lesion in the course of known diabetes. Shea et al.,[14] in a statistical study, were able to obtain only a low degree of positive correlation between the severity of the nephropathy at the time of autopsy and the known duration of diabetes. These authors state that their data fit well with the concept that all cases of nephropathy tend to become more severe with the passage

* Received for publication October 26, 1960.

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Presented at the meeting of the American Federation for Clinical Research, Atlantic City, New Jersey, May 1, 1960.

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† This study was carried out under Diabetic Teaching Grant No. 2A-5063, National Institute of Arthritis and Metabolic Disease. Support was also provided by Grant No. A-2563, National Institutes of Health; Eli Lilly & Company, the Texas State Department of Health; the Harris County Health Unit, and the Houston Heart Association Grant No. 603-9.

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of time, but that some cases progress rapidly and some slowly. All investigators comment on the difficulty of determining the time of onset of the characteristic carbohydrate defect.

The presence of nodular intercapillary glomerulosclerosis is specific or nearly specific for diabetes.[10, 15] Some disagree,[16–18] but generally most authors state that the "advanced" or "severe" lesions are seen only in patients with diabetes. Diffuse capillary glomerulosclerosis, as described by Bell,[19] is regarded as being much less specific, but its presence is frequently correlated with diabetes mellitus.[15, 20] Bell has commented on the difficulty of distinguishing between the diffuse and the minimal nodular lesions.[20] Autopsy studies have shown that microscopic evidence of nodular glomerulosclerosis was present in the kidneys of diabetic patients who had no clinical evidence of renal involvement.[21]

Significantly, a number of autopsy studies of diabetic glomerulosclerosis include at least one case with typical lesions in a patient not known to be diabetic.[12, 13, 22–28] Some investigators have hypothesized that glomerulosclerosis is not specific for diabetes,[16, 17] others that the diabetes has been present but has ameliorated,[23, 29] and yet others feel that the diabetes has been mild and undetected.[12, 13] If such patients can be shown to be prediabetic (e.g., normal glucose tolerance in a patient who will later develop overt diabetes), this would provide strong support for the thesis that the genesis of the renal vascular lesion is independent of the overt carbohydrate defect, and that both the vascular and carbohydrate defects are component parts of the diabetic syndrome.

The advanced renal lesions of diabetes mellitus have been well described in autopsy material[10, 19] and in renal biopsy studies,[7, 15, 30, 31] whereas few biopsy studies of the early changes in diabetes have been reported.[5, 7, 15] Excepting the investigations of Arnold et al.[5] there are no studies available of the renal changes in prediabetes and latent diabetes.

Adequate comprehension of the pathogenesis of diabetic nephropathy is impossible without an investigation of the earliest changes in the glomerular capillary of the diabetic.

Methods and Materials

Renal biopsy was performed by a modification of the method of Muehrcke et al.[32] Seventy renal biopsies adequate for histologic assessment were available on 62 patients, including overt diabetics, latent diabetics, and prediabetics.

All renal tissues were examined by light microscopy, using hematoxylin-eosin and periodic acid-Schiff technics as the screening procedures. Special stains and staining methods, including Masson's trichrome, silver methenamine, periodic acid-silver methenamine modification of Jones, alcian blue, phosphotungstic acid hematoxylin, Verhoeff's and Van Gieson's methods for elastic tissue, and Bielchowsky's method for reticulum (Foot's modification)

were used when they were deemed to be necessary. In six selected patients, including four with minimal basement membrane thickening as detected by light microscopy, a portion of the renal biopsy tissue was also examined by electron microscopy.*

Blood sugar was determined by the method of Somogyi and Nelson. During the three days prior to the glucose tolerance test each patient was fed a diet containing 300 gm. of carbohydrate.[33] Glucose was administered orally in the amount of 1.75 gm./Kg. of body weight, with a maximum of 100 gm. The upper limits of normal for the blood sugar values in the standard glucose tolerance test were: fasting, 95 mg.%; 30 minutes, and one hour, 139 mg.%; and two hours, 119 mg.%. The glucose tolerance test was considered to be abnormal when either the 30-minute or one-hour value was elevated, in addition to elevation of the two-hour value. For the steroid provocative test each patient received 30 mg. of prednisone or prednisolone from eight to eight and one-half hours prior to the glucose tolerance test. This is a modification of the Fajans-Conn test [34, 35] in which the total dose of prednisone was given at one time. West [36] has shown that the maximal effect of the steroid on carbohydrate metabolism occurs at approximately eight hours. The steroid test was considered to be abnormal when the 30-minute or the 60-minute specimen exceeded 159 mg.%, and the two-hour specimen exceeded 139 mg.%.

TABLE 1

Analysis of the Groups of Diabetic Patients by Age, Duration of Known Carbohydrate Defect, and Sex

Groups	Mean Age ±S.E.M.*	Average Duration of Diabetes ±S.E.M.*	Number of Patients	
			Male	Female
1. Prediabetes	45.1 ± 3.6	Unknown	5	6
2. Less than one year	51.3 ± 3.8	†0.3 ± 0.4	7	5
3. One to five years	51.5 ± 3.8	3.1 ± 0.3	10	8
4. Six to 10 years	49.8 ± 3.7	8.7 ± 0.5	3	5
5. Eleven to 39 years	45.5 ± 3.7	16.9 ± 2.2	7	6
Total	48.9 ± 1.8	7.7 ± 1.6	32	30

* Standard error of the mean.
† Excludes six patients selected in the same way as Group 1, but in whom no provocation with cortisone was needed.

The diabetic patients studied by renal biopsy were grouped according to the known duration of the carbohydrate defect (Table 1). Group 1 includes 11 patients classified as being prediabetic. None of these patients had a past history of diabetes. Seven were selected for biopsy on the basis of stigmata suggesting the presence of diabetes, such as family history,[34]

* Performed by Mr. Dale Gulledge under the direction of Dr. James C. Hampton, Department of Anatomy, Baylor University College of Medicine.

presence of premature vascular aging,[37] and fetal oversize.[38, 39] The complete list is summarized in Table 2. These criteria for the diagnosis of prediabetes, including normal glucose tolerance and abnormal provocative glucose tolerance, as well as family history and certain complications of pregnancy, are in agreement with the definition of prediabetes as given by Conn and Fajans,[34, 35] and Jackson.[39] In this study, however, this concept was extended to include premature vascular degeneration, hypercholesterolemia, functional hypoglycemia, and chronic or recurrent urinary tract infection, all of which we have found to be very useful indicators of the prediabetic state in persons in the 30- to 55-year-old group.

The remaining four patients (cases 5, 7, 8, and 9) were not suspected clinically, but were included in this study after renal biopsy, done for reasons other than this investigation, had shown features of early diabetic

TABLE 2

Occurrence of Various Stigmata Suggesting Diabetes Mellitus in the 11 Prediabetic Patients

Stigmata Suggesting Diabetes Mellitus	Case 1 L.B. NF Age 34	Case 2 O.E. WM Age 43	Case 3 C.E. WF Age 50	Case 4 L.H. NM Age 17	Case 5 H.F. NM Age 43	Case 6 O.I. WF Age 60	Case 7 M.R. NM Age 56	Case 8 F.R. WM Age 55	Case 9 F.S. NF Age 49	Case 10 A.S. WF Age 50	Case 11 J.T. WF Age 33
1. Family history of diabetes	0	0	+	0	0	0	0	0	+	+	+
*2. Premature vascular disease											
a. Personal	0	+	+	0	0	+	0	+	+	0	0
b. Familial	0	0	+	0	0	0	0	0	0	0	0
3. History of transient glycosuria under stress	+	0	0	+	0	0	0	+	0	+	0
4. Functional hypoglycemia	0	0	0	+	0	+	0	0	0	+	0
5. Fetal oversize	0	0	+	0	0	0	0	0	+	0	0
6. Microaneurysms	+	0	+	0	0	0	0	0	+	0	0
7. Hypercholesterolemia	+	+	+	+	0	+	+	+	+	+	0
8. Xanthelasma	0	0	+	0	0	0	0	+	0	+	0
9. Pyelonephritis	+	0	0	0	+	0	+	+	+	0	+

* Onset of arteriosclerotic heart disease, cerebral thrombosis, or occlusive arterial disease of the lower extremities prior to 55 years of age.

glomerulosclerosis. It should be noted that only one of these patients was free of stigmata and that two (cases 8 and 9) should have been suspected clinically. Each of the 11 patients was studied by means of a standard glucose tolerance test and a steroid provocative glucose tolerance test. Asymptomatic azotemia was present in one patient (case 8); the remaining 10 patients were in apparent good health, and were not hospitalized at the time of the study. The results were felt to be accurate reflections of carbohydrate tolerance.[40] These cases were carefully evaluated to rule out the possibility of amelioration of diabetes such as that reported by Collens et al.[41]

The mean values for the standard and provocative glucose tolerance tests are summarized in Table 3. In standard glucose tolerance tests two patients showed blood sugar values between 140 and 160 mg.% within the first hour, but none of the 11 patients showed values of 120 mg.% or greater at two

hours. All patients exceeded the upper limits of normal for the steroid provocative test.

Group 2 consisted of 12 patients. Six of these patients were also selected on the basis of stigmata suggesting the presence of diabetes; subsequently, carbohydrate intolerance typical of diabetes was manifested in the standard glucose tolerance test. This type of patient is often regarded as being a latent diabetic. The six remaining patients in Group 2 were frank diabetics, who were studied within a period of one year after the diagnosis was established on the basis of glycosuria and grossly elevated blood sugars, either while fasting or after carbohydrate ingestion. All six of these patients were receiving therapy in the form of insulin or one of the oral hypoglycemic agents. These 12 patients were grouped together because they were representative of the earliest diagnosable carbohydrate defect. The true duration of the hyperglycemia was unknown, and the duration of the diabetes could be dated only from the time of the first abnormal glucose tolerance test.

TABLE 3

Mean ± Standard Error of the Mean for the Standard and the Steroid Provocative Glucose Tolerance Tests in the 11 Prediabetic Patients

Tests	Fasting	½ Hour	1 Hour	2 Hours	3 Hours
Standard	70.5 ± 3.8*	126.1 ± 10.8	119.9 ± 8.2	99.2 ± 8.4	83.3 ± 7.9
Provocative	103.6 ± 5.6	168.4 ± 6.2	199.6 ± 11.3	178.1 ± 8.0	115.8 ± 7.5

* Standard error of the mean.
Normal fasting blood sugar, Somogyi-Nelson method: 60–96 mg. %.

Groups 3, 4, and 5 included known diabetics classified according to increasing duration of known diabetes. Group 5 included patients with diabetes of 20, 29, and 39 years' duration. The status of the carbohydrate defect ranged from uncontrolled to well controlled, and the treatment programs from virtually none to closely controlled dietary management, with or without insulin or oral agents. The severity of the carbohydrate defect varied from the very mild to the most severe.

RESULTS AND DISCUSSION

The glomerular changes in the biopsy material as seen under light microscopy were graded minimal, moderate, and marked. Grading was based on the degree of glomerular basement membrane thickening, and on the proportion of glomeruli affected.

Renal tissues obtained from all 62 patients showed varying degrees of glomerular basement membrane thickening; of these, 37 were assessed as having minimal nephropathy. This minimal thickening was confirmed by electron microscopy in four patients in whom the light microscopy thickening of the basement membranes was least obvious. In each instance, the

basement membrane measured 6,000 to 9,000 Angström units by electron microscopy, about two to three times normal thickness. This thickening, as seen by electron microscopy, is similar to the basement membrane changes in the diabetic kidney reported by Farquhar et al.,[42] Bergstrand and Bucht,[43, 44] and Goetz et al.,[45] using similar technics.

The following case is illustrative of the minimal renal changes. A 59-year-old male was admitted to the hospital with a diagnosis of pyelonephritis. The urine specimen obtained on admission revealed 1-plus glycosuria. Subsequent urinalyses showed no evidence of sugar. Some weeks later, when the patient was in good condition following recovery from the acute infection, and after a three-day preparatory diet, the standard glucose tolerance

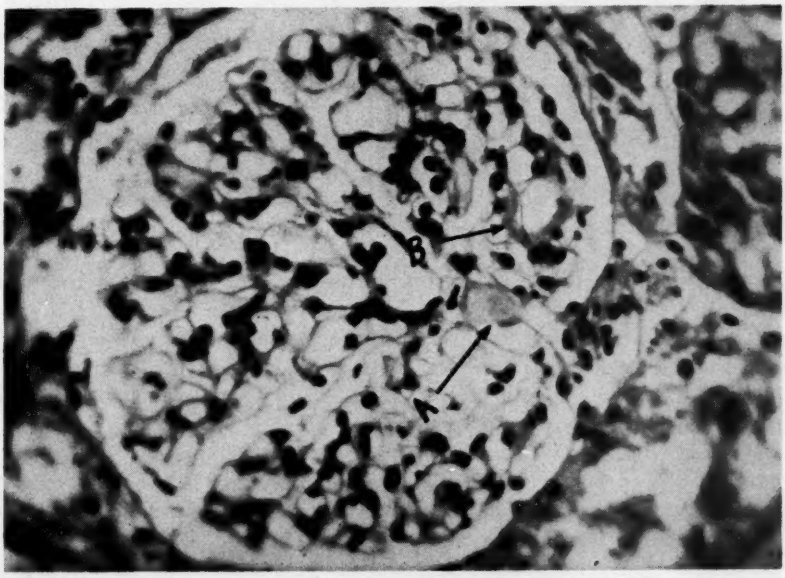

FIG. 1. (H&E). A. Minimal nodular lesion. B. Minimal diffuse thickening.

test showed a diabetic configuration. A percutaneous renal biopsy was done. In the hematoxylin-eosin preparation local minimal diffuse basement membrane thickening of glomerular capillaries was observed in a number of sections of the biopsy (Figure 1A). The localized nodular intracapillary lesion at the hilus of this glomerulus (Figure 1B) has been observed frequently in these cases, but it has been seen, also, not infrequently in other renal biopsy tissues from patients with hypertensive arteriolar renal disease and in patients with glomerulonephritis. Figure 2, from the periodic acid-Schiff preparations, demonstrates more clearly this local thickening of various areas in the glomerular capillaries. Figure 3, an electron photo-

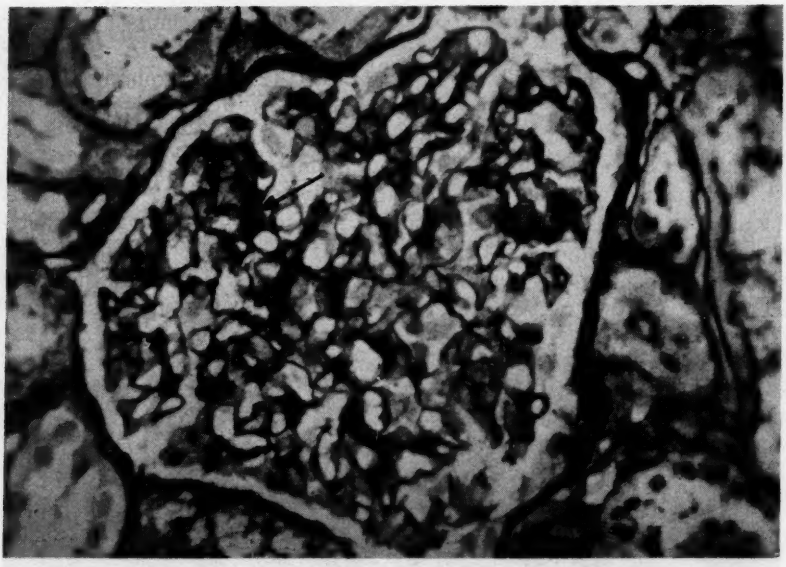

FIG. 2. (PAS). Arrow indicates an area of minimal diffuse thickening.

micrograph of this biopsy, confirms the presence of glomerular basement membrane thickening of twice or thrice normal dimensions.

Ten patients were felt to have moderate glomerular changes and 15 patients showed marked glomerular changes of the classic type described in the literature. One example of each was studied by electron microscopy, confirming the light microscopy observations.

The Kimmelstiel-Wilson lesion, or nodular glomerulosclerosis, was found in 50% of the cases studied (Table 4). Nodular lesions were always found in association with the diffuse type of glomerular basement membrane thickening, this finding again confirming the observations of other

TABLE 4

Incidence of Bell's Diffuse Lesion, Kimmelstiel-Wilson Nodular Lesion, Barrie's Exudative Lesion, and Pyelonephritis

Groups	Number of Patients	Bell's	*K-W	Barrie's	Pyelonephritis
1. Prediabetes	11	11	4	4	5
2. Less than 1 year	12	12	3	7	4
3. 1 to 5 years	18	18	7	7	8
4. 6 to 10 years	8	8	8	8	7
5. 11 to 39 years	13	13	9	12	7
Total %	62	62 100%	31 50%	38 61.3%	31 50%

* Kimmelstiel-Wilson.

workers.[15, 20] Diffuse membranous thickening of the type described by Bell[19] was seen in all 62 patients studied. As noted previously, in 37 cases the changes were minimal. The "exudative" ("fibrinoid") lesions in the form of hilar "fibrinoid" mesangial lesions, "fibrin caps," and "capsular drops" (which we refer to as Barrie's lesions, since we feel that they were best described by Barrie,[46] although others have paid considerable attention to them)[47] were seen in 38 cases. These exudative lesions were seen in 80% of the inadequately controlled diabetic patients, in 47% of the well controlled diabetics, and in 36% of the prediabetics.

FIG. 3. Electron photomicrograph of a portion of the glomerulus. The basement membrane is thickened to about 2 × normal. Arrow indicates an area measuring 9,000 Å, about 3 × normal.

The renal changes observed in this investigation seem to be a constant accompaniment of the diabetic syndrome, and in approximately 300 percutaneous renal biopsies performed at Jefferson Davis Hospital similar lesions have not been encountered in nondiabetics. When these lesions are seen in patients who are not known to have diabetes, further tests of carbohydrate metabolism are indicated, as well as long term follow-up of the patient.

The presence of minimal lesions in all cases in this series was unexpected

in view of the earlier reports.[12, 16, 17] However, a much higher incidence of glomerular lesions than previously reported has been found in recent studies by Gellman et al.,[15] who report diffuse lesions in 75% of 53 patients studied by renal biopsy, and in all nine of their patients who were autopsied. Brun et al.[30] have also reported diffuse lesions in 11 of 12 diabetic patients studied by means of renal biopsy, while Goetz et al.[45] have observed the typical glomerular basement membrane thickening in two diabetics of less than two years' duration.

Excluding the prediabetics, there is a steady and progressive increase in the severity and frequency of the vascular lesions as observed in the afferent arterioles and the interlobular, arcuate, and subarcuate arteries, with increasing duration of the diabetes (Table 5). This finding is in agreement with previous reports.[10, 20] The relatively high incidence of severe vascular changes in the prediabetics in our series is apparently related to the fact that

TABLE 5

Renal Arteriolar and Arterial Changes Detected by Kidney Biopsy in Patients with Diabetes Mellitus

Groups	Number of Patients Biopsied	Fibrinoid Change		Hyperplastic Sclerosis Interlobular Art.	Atheroma Arcuate Art.
		Afferent Art.	Efferent Art.		
1	11	70% (7/10)*	22% (2/9)*	80% (8/10)*	83% (5/6)*
2	12	50% (6/12)	25% (2/8)	82% (9/11)	50% (4/8)
3	18	88% (15/17)	46% (6/13)	94% (16/17)	100% (3/3)
4	8	100% (8/8)	86% (6/7)	100% (8/8)	100% (2/2)
5	13	100% (13/13)	82% (9/12)	100% (12/12)	100% (4/4)
Total	62	82% (49/60)	52% (25/48)	91% (53/58)	78% (18/23)

* The figures in parentheses indicate the number of patients with vascular changes and the number of patients from whom biopsies yielded sufficient vascular material for assessment.

we have selected for study a group of patients in whom diabetes was suspected largely because of the presence of premature arterial disease.

The data in Figure 4 indicate that, although there is a tendency for progression of the renal lesions with increasing duration of the carbohydrate defect, noteworthy exceptions are encountered in poorly controlled diabetics of 20, 29, and 39 years' duration, who had only minimal nephropathy. These findings are in agreement with the reports of Hagedorn,[48] Miller and Reeves,[49] and West.[50] On the other hand, two prediabetics and two overt diabetics of less than one year's duration demonstrated moderate to marked nephropathy. These observations are corroborated by Shea et al.,[14] who conclude that diabetic renal lesions tend to progress with time, in some instances quite rapidly, and in other instances quite slowly. It would appear that the progression of the glomerular lesions is affected in part by the severity and control of the carbohydrate defect, but as yet unknown hereditary and metabolic factors are of major importance. Our data also support

the conclusion of several investigators that the genesis of the vascular disease and control of the carbohydrate defect are independent of each other.[4-6] Colwell [51] has postulated that the carbohydrate defect in diabetes begins at birth. Our results are in substantial agreement, as they suggest that the vascular component of diabetes begins years before detectable clinical evidence of either the vascular or the overt carbohydrate abnormality. Our results are also in agreement with the work of Ditzel et al.,[8] who showed that there was a high incidence of vascular changes in the conjunctivae of

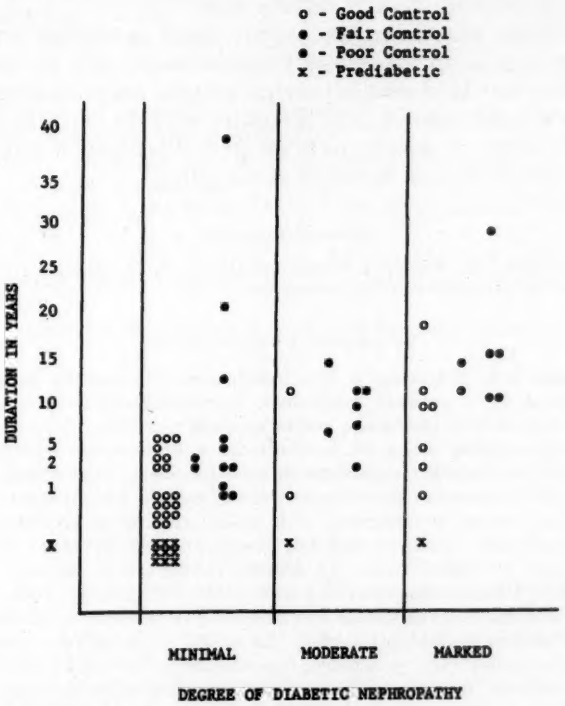

FIG. 4. Severity of the renal lesions tends to increase with greater duration of the diabetes mellitus. However, three patients with minimal lesions had had diabetes for many years (first column).

children born of diabetic mothers. These authors concluded that the vascular changes were probably related to factors other than the detectable or chemical carbohydrate defect.

Our study with kidney biopsy supports the concept that diabetes mellitus is a multifaceted metabolic defect (to date recognized only by carbohydrate intolerance), of which the vascular damage and the carbohydrate defect are but two components. In the usual diabetic both of these defects, as

detected clinically, are present in varying degrees. In some patients one component may be present in a major form while the other may be present in a minor form and must be searched for. Careful investigation of this concept is necessary if a clear understanding of the diabetic syndrome is to be gained.

Conclusions

1. This study suggests that diabetic nephropathy seems to be virtually inescapable, once a diagnosis of diabetes mellitus is made either in a prediabetic, latent diabetic, or overt diabetic state.

2. This study has shown that severe renal glomerular and vascular changes can occur in prediabetics and early diabetics and, by contrast, that minimal lesions may be present in poorly controlled diabetes of long duration.

3. With this information it is postulated that the nephropathy and the carbohydrate defect of diabetes mellitus are independent of each other, but evolve from the same basic metabolic abnormality.

Acknowledgments

We wish to thank Dr. Robert A. Hettig and Dr. C. W. Daeschner for their assistance and criticism in the preparation of this manuscript.

Summario in Interlingua

Alterationes in le glomerulos e vasos renal esseva studiate per medio de biopsia renal in un total de 62 patientes prediabetic, latentemente diabetic, e patentemente diabetic. Le diagnose de prediabete esseva establite per medio del test de tolerantia pro glucosa a provocation cortisonic, in combination con le studio del historia familial e le observation de un presentia prematur de certe processos degeneratori. Un diffuse spissification del membrana basilar de glomerulo, visibile per microscopia a lumine, esseva presente in omne le specimens. Isto esseva confirmate per microscopia electronic in 6 patientes. Lesiones nodular esseva presente in omne le gruppos de patientes, incluse le prediabeticos. Le mesmo valeva pro le lesiones "exsudative" (fibrinoide) e le lesiones reno-arterial e arteriolar. Le presente studio suggere que nephropathia diabetic es virtualmente inevitabile e pote preceder le defecto de hydrato de carbon in diabete mellite per multo. Le studio etiam monstra que le lesiones vascular e glomerular pote progreder rapidemente in ben-stabilisate diabeticos e progreder lentemente in mal-stabilisate diabeticos. Iste observationes suggere que le nephropathia e le defecto de hydrato de carbon es mutualmente independente sed qu illos se disveloppa ab le mesme anormalitate metabolic fundamental.

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THE QUANTITATIVE MECHANISM AND THE SENSORY RECEPTOR ORGAN OF HUMAN TEMPERATURE CONTROL IN WARM ENVIRONMENT *

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THE measurement of human body temperature is perhaps the only instance where a quantitative method of clinical observation is routinely applied in every family, by every mother. Yet we are far from understanding its meaning. The measurement is performed in disease, not during health. In health, human body temperature is homeostatically regulated by physiologic mechanisms, which have been the goal of many attempts at discovery. How does it happen, that in summer or in winter, at peaceful rest or with the metabolic furnace at full blast during strenuous exercise, our temperature is always approximately 37° C?

It has long been realized that some specific mechanism must be performing this task, and a conclusive experiment has shown as early as 1885 that this mechanism is neural. What are the necessary component parts of a neural servomechanism in physiology? There must be three. First, sensory receptor organs are required to receive the stimulus (in our example, a deviation of temperature), a physical phenomenon, and to translate it into sensory nerve impulses, a phenomenon of life. Second, there must be a "center" in the nervous system to translate by synaptic transmission any set of afferent, sensory impulses into a set of efferent, effector nerve impulses. Third, there must be effector organs which act to reduce or abolish the stimulus both at the site of sensory reception and elsewhere. This means, in the present example, that the temperature of the human body will be restored to a normal level from any aberrations toward hot or cold.

For the regulation of human temperature in cold environment, Max Rubner [1] in 1900 identified increased chemical (metabolic) activity as the only autonomic mechanism. (Chemical heat regulation is not a topic of this paper). In a warm environment, temperature regulation is achieved by two autonomic effector mechanisms: the sweat glands and the peripheral blood vessels. Vasodilatation facilitates heat transfer and enables heat, the waste product of our metabolic reactions, to go from the interior of the body to its surface. Sweating continues the process of heat loss.

* Received for publication May 9, 1960.
From the Naval Medical Research Institute, Bethesda, Maryland.
Presented at the Forty-first Annual Meeting of The American College of Physicians, San Francisco, Calif., April 4-8, 1960.
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Sweat glands pour out water upon our skin, and in the transition of this water from the liquid to the vapor state, 560 calories of heat per gram are absorbed—a very efficient way of making the undesirable excess of energy disappear. The energy is tucked away in the physicochemical storehouse of water vapor, and carried off by convection and diffusion.

The cerebral center, where the incoming sensory impulses (or messages) are translated into outgoing impulses (or orders) for the sweat glands and the blood vessels, was identified in a series of discoveries that began in 1885. At that time, Aronsohn and Sachs [2] in Vienna punctured the brains of experimental animals and found that body temperature went out of control after lesions were produced in the anterior basal regions. A specific sensitivity of the brain to temperature, rather than to lesions, was discovered by Kahn [3] in 1904. He found that heating the head of a dog made its body temperature fall, whereas cooling the head produced a rise in body temperature. In 1912, an American investigator, Barbour,[4] while working in Vienna, identified a region at the base of the brain by direct thermal stimulation as one sensitive to temperature and as producing meaningful thermoregulatory responses. Later, Ranson and Magoun [5] in 1938 outlined an accurate map of heat-sensitive structures in the anterior hypothalamus. Von Euler [6] in 1950 even recorded steady action potentials commensurate with the stimulus of temperature from this part of the brain.

On the basis of these findings, there could be no doubt that man has not one but two nervous structures which are influenced by temperature: the hypothalamus, just described, and millions of receptor endings in the skin, known from everyday experience to be the site of temperature sensations, warm or cold. In which of these two structures do the nervous impulses originate that initiate and maintain the autonomic activity of the sweat glands and the dilatation of the peripheral vessels in response to warm environment?

Teachers of classical temperature physiology contended (and taught the medical student) that the autonomic responses of sweat glands and blood vessels are elicited from the skin by afferent impulses to the hypothalamus, that they originate in cutaneous thermoreceptors, and that the temperature of the hypothalamus itself exerts some additional influence, possibly by changing the sensitivity of the center to the impulses coming from the skin. The "dual control" theory of human temperature control is accepted in current monographs and textbooks.

This paper will present recent experimental evidence [7] that this view, so far as it concerns the regulation of human temperatures in warm environment, is in error. Actually, the sweat glands obey exclusively the orders of internal, not external (cutaneous), temperature changes, and the blood vessels of the skin behave in the same way (except for some direct influence of temperature upon blood vessels, which occurs in the absence of skin thermoreceptors and after disconnection of the hypothalamus). The conse-

quences of this statement are far-reaching. It means that the anterior site of the so-called heat "centers" in the hypothalamus is more than a relay station for afferent impulses from the skin. Since it acts without such afferent impulses, it must be considered a terminal sensory organ, containing first neurons for temperature reception. It behaves like an "eye" for temperature, comparable to the optical eye, the retina, our sensory organ for light.* (The optical and thermal "eyes" are closely related anatomically. Both of them are outgrowths of the bottom of the third ventricle. The optical eye during its develcpmental history bulges out and forms a double-walled cup, while the "thermal eye" stays in its original place, the hypothalamus.)

In the approach to understanding this rather fundamental problem of human existence in the many climates of our earth and at many levels of metabolic activity, in health and in disease, the first step was, as usual, the asking of a question, or raising of a doubt: Why (in engineering terms) should a house be air-conditioned and heated by distribution of thousands of contact thermometers over its outside walls? If the internal temperature in the living room were to be regulated, would not one thermostat in the living room suffice to operate furnace, fan, and refrigeration from that site? This would seem feasible whether in summer heat, in winter cold, or with the metabolic heat produced by many guests gathered in the living room for a party. On the other hand, thermometers on the outside wall would not work properly by themselves, since they cannot possibly "see" the internal temperature. Neither in life nor in technology can a quantity be regulated unless it is first measured.

The second step was a development of new methods for the measurement of stimuli and responses. They would enable the investigator to analyze the system on the intact human body during vigorous thermoregulatory action, for it was not planned to seek the answer in animal experiments through graded destruction of the components such as sensory organs, neural pathways, centers, or effector mechanisms.

To measure the three responses of temperature regulation, namely, sweat secretion, vasodilatation, and increased metabolic heat production, the method of "gradient calorimetry" was successfully tested after ten years' effort at the Naval Medical Research Institute in Bethesda.[10] Figure 1 shows the principle of gradient calorimetry: in a cavity or black body, thousands of thermocouples measure and integrate the total flux of metabolic energy by sensing heat flow rate as a tiny difference in temperature across a "gradient layer." This measurement is independent of the size, shape,

* It has been occasionally contended that these conclusions are not yet fully justified, since it is not impossible, no matter how unlikely, that other, as yet undiscovered, thermoreceptor fields exist in regions of internal cranial temperature. However, by thermal, not electrical stimulations, meaningful responses have been elicited specifically from the anterior hypothalamic site by Hemingway et al.[8] and by Freeman and Davies.[9] Combined with these observations the calorimetric data would establish a central terminal receptor function at this site, even though additional internal thermoreceptors might some day be discovered.

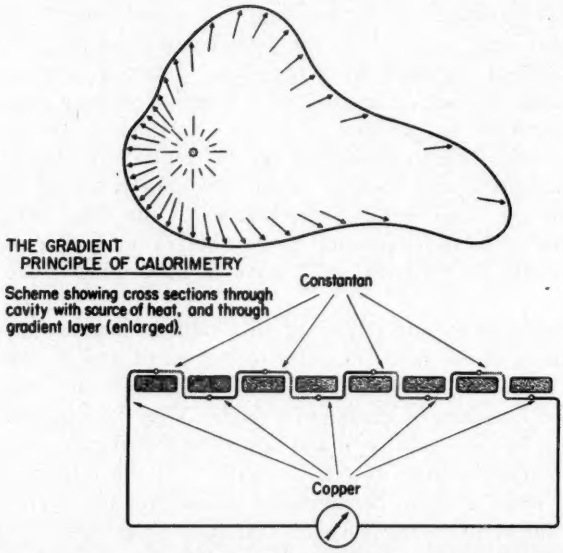

FIG. 1. Principle of gradient calorimetry. In a cavity (above) uniformly lined with a "gradient layer" (below, enlarged), output of a source of energy is correctly measured and continuously and rapidly recorded, regardless of its size, shape, location, or surface characteristics.

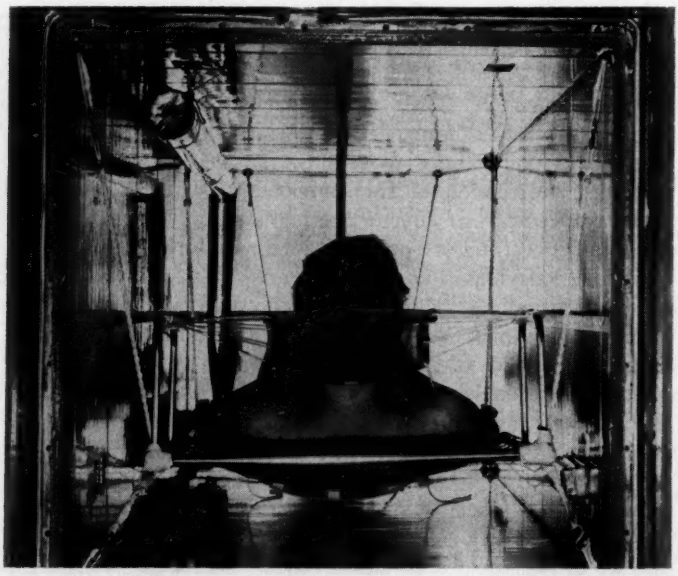

FIG. 2. Human subject in a gradient calorimeter. The subject is suspended for minimal direct conduction. The gradient layers are covered with anodized aluminum foil, absorptive for infrared thermal radiation.

location, angular position, and surface characteristics of the object and the instrument. This principle has been applied to the construction of the gradient calorimeter for the human subject, as shown in Figure 2. Additional instrumentation permits us to measure separately the evaporative component of the heat loss (which after subtraction of a small and almost constant contribution from the lungs is sweat gland activity) while blood flow through the skin is measured calorimetrically as "thermal conductance" (Figure 3). The recordings are continuous. The response of the instrument is quite rapid to changes of conduction or evaporation, and almost instantaneous to changes of radiated heat loss. It has thus become

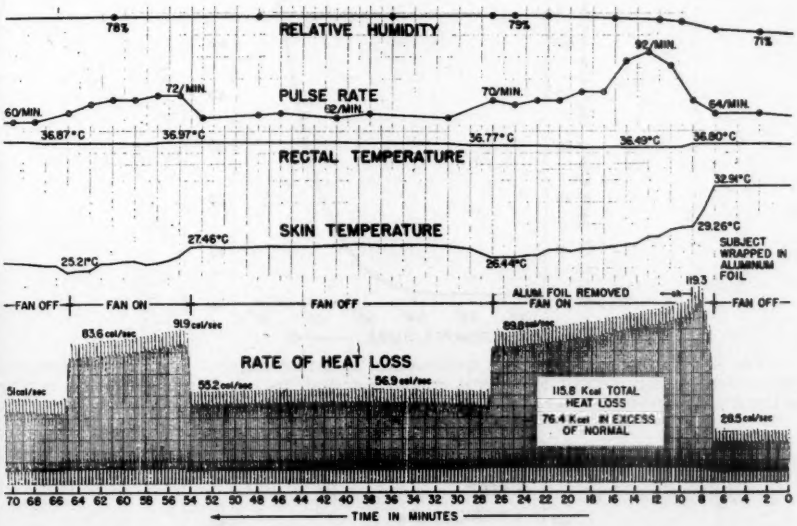

FIG. 3. Recording by gradient calorimetry. Radiated, conducted, convected, and evaporative heat losses are simultaneously recorded. With minimal distortion, rapid events in human energy exchange are followed. In this record, instantaneous changes were brought about and followed by the measurement with sudden introduction or elimination of forced air convection or by uncovering a human body previously covered with reflective aluminum foil in a cool environment.

possible to establish and to observe steady states as well as to measure the responses of sweat glands and blood vessels during fairly rapid, transient changes in heat transfer.

The third step in approaching the problem was to construct an experimental design, an argument of simple logic, to permit an unequivocal answer to the question: Is the skin, or is the hypothalamus, or are both of these organs or neither of them, origins of the sensory impulses by which sweat glands and blood vessels are driven into thermoregulatory action? (So far as the author can see, this question has not previously been asked in such a way that experiments could give the answer.) The argument that shall

be used here goes as follows: Human body temperature can be maintained throughout our lifetime at the same normal level only if the apparatus of regulation has reasonably stable and reproducible characteristics, only if, for example, the response of sweating begins always at the same "set-point" of temperature, a threshold value, and only if sweating increases reproducibly in quantity, with increasing thermal stimulation. In other words, a firm and reproducible relation *must* exist between the temperature at the sensory

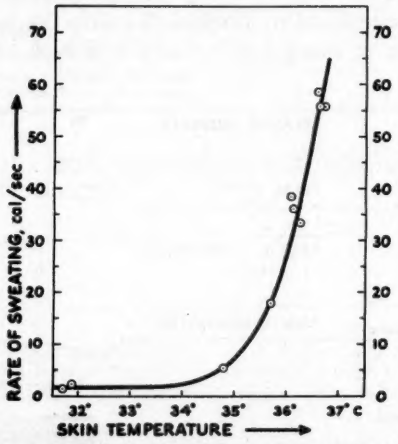

FIG. 4A. Sweating versus skin temperature of resting subject. At rest, skin temperature is reproducibly related to internal cranial temperatures. A false coincidental relation is therefore observed between skin temperature and the rate of sweating.

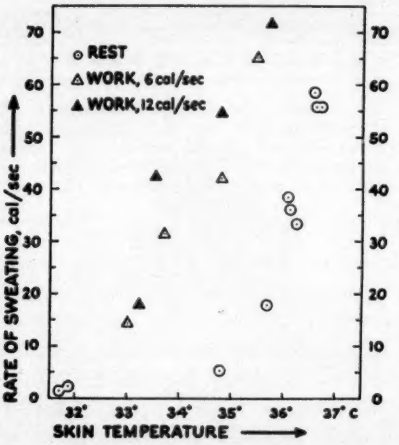

FIG. 4B. Sweating versus skin temperature on resting or working subject. Physical exercise dissociates the normal relationship of internal cranial and skin temperatures. No meaningful relation is observed under these conditions between skin temperature and the rate of sweating.

receptor organ (not elsewhere!) and the rate of sweating. If the skin is the receptor organ, we must find such a relation with skin temperature. If the hypothalamus is the receptor organ, we must find such a relation with internal, hypothalamic temperature. If both the skin and the hypothalamus are sources of impulses to the sweat glands, no meaningful and reproducible relation between the response and any one of the two stimuli will be found, as soon as both temperatures are arbitrarily and independently changed, at

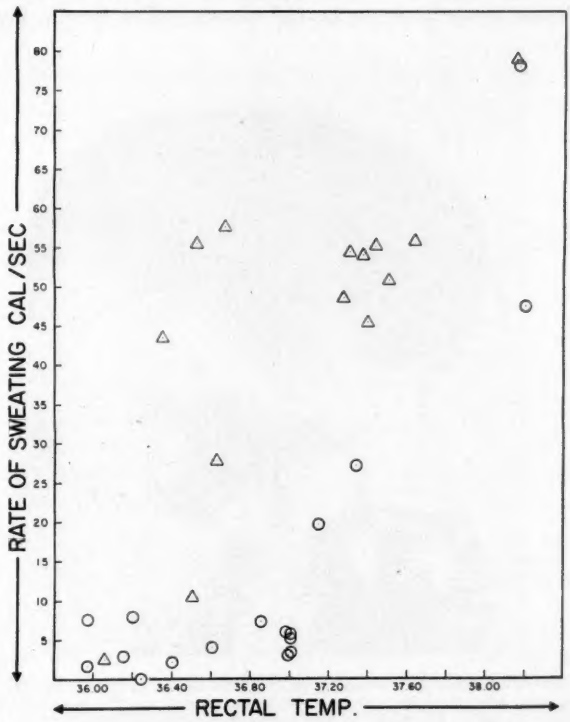

FIG. 5. Sweating versus rectal temperature. No meaningful relation is observed between the rate of sweating and internal temperature measured in the rectum. (Rectal temperatures differ widely from internal cranial temperatures which are related to the rate of sweating.)

different intensities or in opposite directions. For, whatever relation existed between the response and one of the two stimuli would then be destroyed by the arbitrary changes of the other, and vice versa. This may be shown with a series of measurements of cutaneous stimuli and sweat gland responses on one subject in many different climates, ranging from moderately cold (plus 10° C.), to very hot (plus 45° C.) in steady states (Figure 4A). As long as all the experiments are carried out at rest, a co-

incidental relationship is observed. For with the subject at rest, in a defined environment, hypothalamic temperature is in a firm relation to skin temperature. However, as soon as this coincidental relation is destroyed in additional tests involving physical exercise (Figure 4B) (which dissociates the internal and the cutaneous temperatures), the graph becomes entirely senseless. It is obviously disrupted by the effects of increased internal temperature upon the rate of sweating during exercise. All working observations are shifted to the left, or upward. The well known influence of internal temperature is hereby shown. The graph, however, does

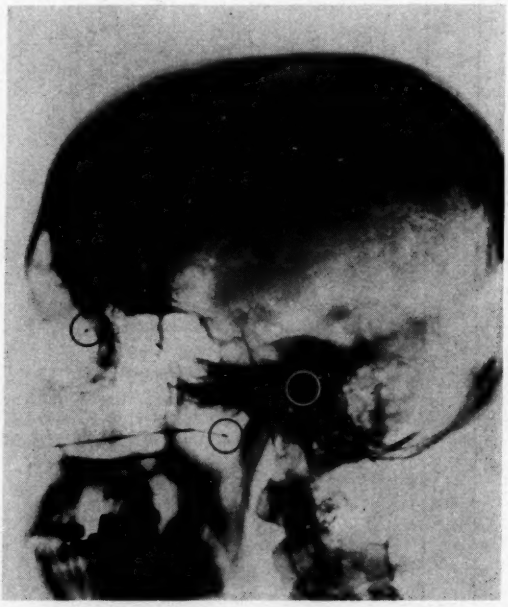

FIG. 6. Thermocouples in various cranial locations. For the recordings of Fig. 7 thermocouples were placed in the anterior ethmoidal region, at the tympanic membrane, and in Rosenmüller's fossa, at the stem of the internal carotid artery.

not permit us to say whether or not skin temperature is also a stimulus. It does not, therefore, of itself disprove the classical concept.

Let us now take internal temperature and use the rectal measurement in the classical tradition (Figure 5). In spite of the improved methods for the measurement of sweating a most disorderly plot is obtained, and our question is as far as ever from a solution.

Could it be that more pertinent measurements were required, that in order to determine the causal relation between stimulus and response we would have to modernize not only the measurement of responses, but also the measurement of body temperature? Should we challenge and question

the reliability of the classical measurement in the rectum? This can be done by going into the direct neighborhood of the hypothalamus, without touching or disturbing it, yet close enough for observations in the same area of blood supply, the area of the internal carotid artery.

Figure 6 is an x-ray of the head of an investigator, showing thermocouples placed near the hypothalamus, having been inserted through the upper nasal cavity by an able surgeon. The temperature sensing devices are adjacent to the mucous membranes in three different cranial locations: anterior ethmoidal, Rosenmüller's fossa on the stem of the internal carotid, and at the tympanic membrane in the external auditory canal. All three of these measurements give essentially the same results (Figure 7).* Even during drastic changes of temperature applied from within or from without, the measurements are parallel to one another and should, therefore, when

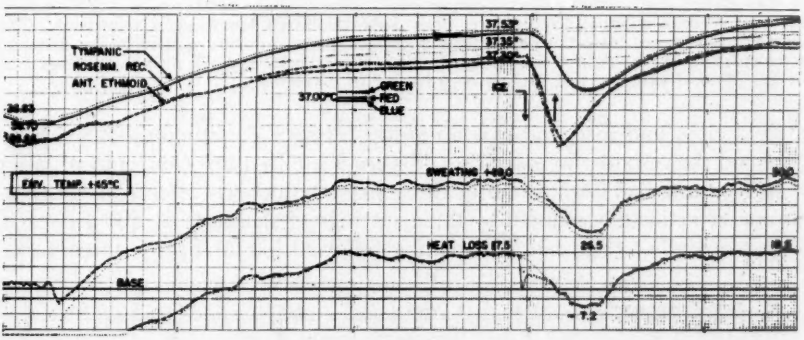

FIG. 7. Temperature recordings from various cranial locations. In spite of a drastic change in environmental temperature (from 29° C. to 45° C.) and subsequent oral ingestion of ice, three widely distant cranial measurements show no essential differences in characteristics.

plotted graphically reveal the same characteristics. (Parallel shifts of absolute temperature are without influence upon the characteristics as outlined above.) Rectal temperature, on the other hand, is very poorly, if at all, correlated to internal cranial temperature (Figure 8). (Under conditions similar to the experiment of Figure 8, classical authors had concluded from rectal measurements that the rate of peripheral blood flow is not related to internal temperature.) Deviations similar to those of Figure 8 may also be demonstrated during exercise or upon oral ingestion of ice, or after putting legs or arms into warm or cold water. Rectal temperature never reflected reliably the patterns of internal cranial temperature changes.

In using internal cranial instead of rectal temperatures we find immedi-

* In the experiments depicted by Figures 6, 7, 8, and 9, the subject was T.H.B., age 55, height 180 cm., weight 68 Kg. L.R.N., age 33, height 175 cm., weight 72.5 Kg., volunteered for the extended series of experiments recorded in Figures 4B and 10, and also for various experiments with cranial measurements similar to those in Figure 6.

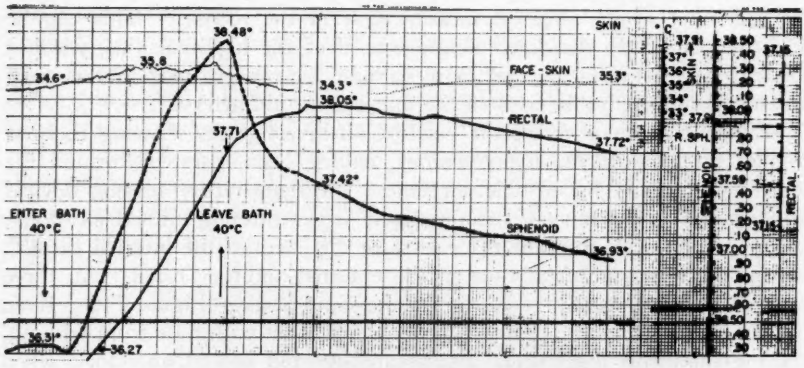

FIG. 8. Failure of rectal temperature to represent cranial temperature as a stimulus of thermoregulatory action. Rectal temperature, conventionally measured, is widely different from cranial internal temperature, desired in studies of temperature regulation. The discrepancies exceed three times the range of physiologic temperature control in this instance, after entering or leaving a 40° C. bath. Similar discrepancies may be shown after ingestion of ice, physical exercise, and cooling or warming of extremities.

ately a close and inseparable relationship between the stimulus of temperature and the response by sweating (Figure 9). In a hot environment, after a steady state had been attained, three sharp reductions of cranial temperature were artificially induced by three servings of sherbert ice, 500 gm. each, ingested orally. The rate of sweating followed like a shadow these varia-

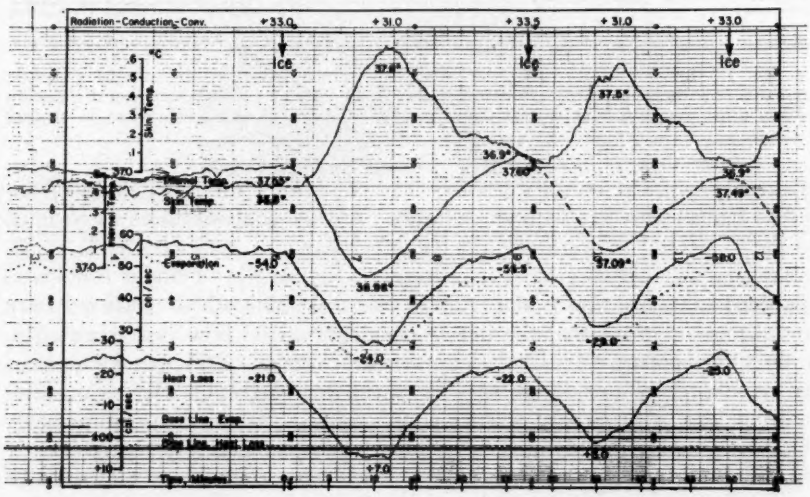

FIG. 9. Rate of sweating in response to cranial internal temperature. Skin and cranial temperatures were oppositely influenced by repeated ingestion of ice. The rate of sweating follows, even in minor details, the internal cranial temperature as a response to cerebral temperature stimulation.

tions even in details. Skin temperature, paradoxically, went the other way. The explanation is that the cooling of the central temperature reduced sweat gland activity. Consequently, the skin became dry and warm in the intensely hot environment. The causal relation between internal cranial temperature as stimulus, and sweat gland activity as response, was thereby demonstrated.

It seemed, therefore, appropriate to replace the unreliable rectal measurements used in Figure 5 with the newly established procedure of measurement at the tympanic membrane, and to carry out a similar new series of experiments using the new technic. The result is shown in Figure 10, and is

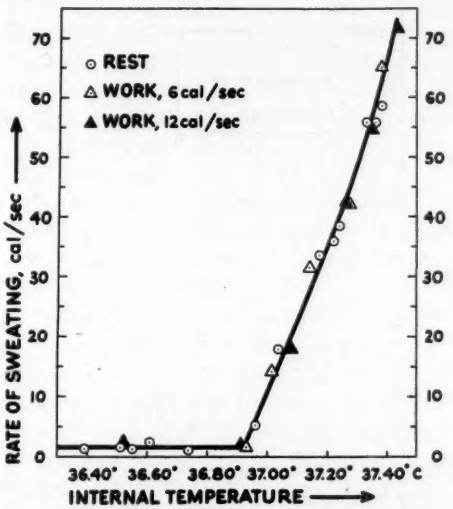

FIG. 10. Sweating in response to cranial internal temperature. Regardless of drastic differences in skin temperatures (see plot of the same experiments against skin temperatures, Figure 4B) the rate of sweating is inseparably related to cranial temperature. The absence of thermoceptor impulses from the skin to the hypothalamic center of sweating is thereby conclusively demonstrated.

the plot long sought for—a quantitative description of the human mechanism of temperature control by sweating. Whether or not the subject exercised, there was always the same relationship between internal cranial temperature and the rate of sweating. In Figures 4B and 10 the same experiments were plotted. As Figure 4B shows, skin and internal temperatures were widely dissociated by arbitrary changes of conditions over the entire range of physiologic control in steady states. The inseparable relation between sweating and internal cranial temperature was unaffected.

In our discussion of this result, it should be borne in mind that any kinds of errors are likely to destroy the remarkable relationship shown in Figure 10. We have seen how the plot was disrupted when the wrong

stimulus was measured (Figure 4B) or when the right stimulus, internal temperature, was measured in the wrong place (Figure 5). Experimental errors in measurements of the stimuli and responses would likewise destroy the order here observed. It is, however, unthinkable that such an order could be simulated or created out of disorder, by any error or incident under the conditions of experimentation. Skin and internal temperatures had been completely dissociated by strenuous exercise by the subject during the experiments (shown graphically as triangles), while the subject rested during the other tests (shown by rings, Figure 4B).

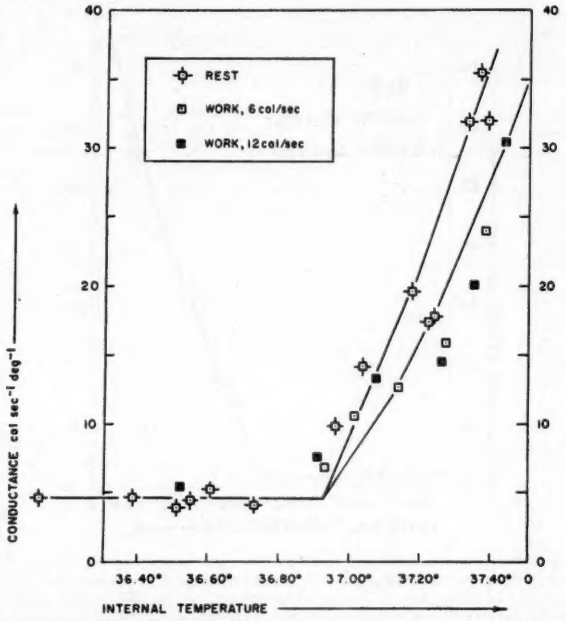

FIG. 11. Peripheral vasodilatation (conductance) plotted against cranial internal temperature. Peripheral vasodilatation is a response to the stimulus of cranial internal temperature. The spread between the working and resting observations is caused by direct—not reflex—effects on skin vessels.

It seems appropriate, therefore, to make the statement that the influence of skin temperature and skin thermoreceptors upon sweating was zero throughout the range of human temperature control for the resting or working subject in this series of experiments, which covered quite well the full range of changing conditions in everyday life.

For vasodilatation, a similar relation can be shown as for sweating, with one important difference: the graph shows (and it was very reassuring to find this difference) the well known direct influence of temperature upon the blood vessels of the skin, which other investigators have demonstrated

after transection of all nervous connections to and from the skin. The appearance of this phenomenon in the graph (Figure 11) demonstrates the validity of the method, while it precludes, on the other hand, a statement quite so rigorous as that given above for the sweat glands, on the absence of skin thermoreceptor impulses.

Summary and Conclusions

A quantitative analysis has been presented of the human mechanism of temperature regulation in warm environment. As a result of this analysis it has been found that afferent impulses from the skin to the sweating mechanism were absent throughout the wide range of conditions observed in the experimental series. Without such impulses, the internal thermoreceptive system was able to maintain, by continued action, sweating rates corresponding to more than two gallons and blood flow rates of more than two tons per day. To increase sweating by one calorie per second and blood flow by 15 ml./min., a rise of only 1/100 of a degree Centigrade in the hypothalamus was required.

In conclusion, a central organ previously identified in classical experiments of neurosurgery now appears to be capable of performing this task without afferent sensory impulses. In its own cells the physical stimulus of temperature must be converted into nervous activity. Therefore, that site, the "heat loss center," cannot be considered merely a synaptic relay station. It must contain a terminal sensory organ with first neurons for temperature perception. This organ seems, therefore, comparable in receptor function, resolving power, and precision, to the retina, our sensory organ for light. It may even send, like the eye, sensory impulses into the sensory cortex for conscious sensations of temperature, although this question is not yet decided. It is through the action of the central receptor organ that the patient with Raynaud's gangrene experiences relief in vasodilatation when he is exposed to environmental heat in a hot chamber. It is warm blood returning from his skin that carriers the message, not the nervous pathway from his skin thermoreceptors, as was previously believed.

But, if the skin has no part in this, what is the function of the millions of cutaneous warm-receptors now disconnected from the autonomic temperature regulating control system? Their task is and remains important. They are, for one, a vital protection against local burns. Second, no doubt they play a major role in letting us know by conscious sensations when it is necessary to move from too warm an environment into another, more comfortable one. Thermoreceptors contribute in letting us know whether to wear a fur coat or a swim suit, whether to build an igloo or a palm leaf hut, whether to be active or inert, whether to curl up or stretch out. This is "Pavlovian" temperature regulation by conscious sensations and willful cortical—not hypothalamic—action of skeletal muscles. "Pavlovian" regulation is powerful but crude, because skin thermoreceptors cannot accurately

observe and, therefore, cannot precisely regulate internal body temperature. Only internal thermoreception can fulfill this function.

It was mentioned at the beginning of this paper that "chemical" heat regulation—the response of man to cold by increased metabolic heat production—was to be excluded from its topics. It must now be stated briefly that no direct analogies can be drawn between "physical" and "chemical" regulation of body temperature. Data from this laboratory will soon be published to show that in cold environment the internal thermoreceptive system exerts its control not by direct stimulation of metabolic activity, but by inhibition of cold impulses originating from skin thermoreceptors.

It remains to be explained why rectal temperature fails the physiologist so completely, and yet is so helpful to the physician and the family doctor. The answer is readily given: The normal regulation of temperature operates over a very narrow range, measured in hundredths of a degree Centigrade. The pathologic aberrations of temperature are one order of magnitude larger —they are measured in tenths of a degree, and, therefore, in clinical diagnosis even rectal temperatures are of considerable value.

Will a refinement of the measurement, i.e., replacement of rectal with tympanic thermometers, lead to refinements of our diagnostic observations? The answer is a conditional "yes." Body temperature as such, no matter how precisely measured, even hypothalamically, is a product of both the environment and the state of the subject or patient. Refined measurements of temperature should therefore be taken under controlled, reproducible conditions. Even better, normal temperature as well as that occurring in fever should be redefined in terms of the set-point, the specific cranial temperature at which the responses of sweating, vasodilatation, or increased oxygen consumption begin to operate. This threshold of the thermochemical apparatus in the brain shifts under the influence of pyrogens. In combination with suitable observations of responses, that is, in terms of "set-point-shift," the measurements would become independent of environmental factors. Human body temperature may then assume its full meaning in physiology, pharmacology, pathology, and clinical diagnosis. But, even if the way to practical applications were long and hard, we still would like to know, for the sake of knowledge, how many senses we have, and how they operate.

ACKNOWLEDGMENT

Gratitude is expressed to H. W. Taylor, M.D., U. S. Naval Hospital, Bethesda, Maryland, for performing the surgical procedures to permit the cranial measurements of temperature described in this paper.

ADDENDUM

While these pages were in press, further experiments in this laboratory have shown a measurable influence of unknown nature by skin temperature upon the rate of sweating. Conclusions concerning total absence of peripheral influences are modified accordingly. Conclusions concerning the predominant thermostatic role of the internal thermoreceptor system are not affected.

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SUMMARIO IN INTERLINGUA

In extensemente variate ambientes calide e a extensemente variate nivellos de activitate metabolic, le responsas e stimulos del human regulation "physic" del calor esseva mesurate con methodos differente ab illos del physiologia classic. (1) Calorimetria de gradiente permitteva le continue e non-distorquite mesuration del responsas sudomotori e vasomotori. (2) Thermometria cranial reimplaciava le pauco fidel mesuration rectal del thermostaticamente regulate temperatura interne. (3) Le correlationes coincidental inter le temperaturas interne e cutanee esseva disrumpite deliberatemente per mesuras experimental.

Esseva trovate que le sudoration a function thermoregulatori es unicamente determinate per le interne temperatura cranial. Impulsos de calor ab le thermoreceptores cutanee non participa in le thermoregulation centro-neural effectuate per sudoration e probabilemente etiam non in ille regulation per vasodilatation. Il seque que le origine central de responsas de perdita de calor ha le proprietates essential de un terminal organo receptori pro temperaturas, comparabile al receptor terminal, i.e. le retina, in le caso del lumine. Le altere mechanismos, i.e. mechanismos pavlovian, del regulation del temperatura in humanos es discutite brevemente. Le potentialitates de thermometria cranial in situationes clinic es delineate summarimente. Constatationes futur in re le thermoregulation "chimic" es mentionate: In ambientes frigide, le thermostato human exerce su regulation del production metabolic de calor per impulsos de calor que age contra le peripheric impulsos de frigido.

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THE PROBLEM OF CLINICAL VASOPRESSIN RESISTANCE: IN VITRO STUDIES * †

By Richard M. Hays, M.D.,‡ *New York, N. Y.*, and Alexander Leaf, M.D.,§ *Boston, Massachusetts*

In recent years, there has been considerable progress in our understanding of the role of antidiuretic hormone in the renal concentrating mechanism. Studies by Hargitay and Kuhn,[1] Wirz,[2] Gottschalk,[3] and others [4-6] have led to our present picture of the mammalian nephron as an efficient countercurrent system. A concentrated urine is formed when antidiuretic hormone alters the permeability of renal tubular cells, permitting the tubular urine to come rapidly into osmotic equilibrium with the hypertonic interstitial fluid of the renal medulla.

Under certain conditions, however, an apparent resistance to the action of antidiuretic hormone may develop. Despite the administration of large amounts of exogenous hormone, the patient or the experimental subject may fail to concentrate his urine. Two such situations are: (1) the reduced response or "escape" from the continuous antidiuretic action of pitressin when this hormone is administered to an overhydrated subject; (2) the impaired ability of many patients depleted of potassium to elaborate a concentrated urine.

This paper describes an in vitro study of the possible mechanisms underlying these two instances of resistance to vasopressin.

Methods

We have recently been studying the action of antidiuretic hormone, vasopressin, on the movement of water across a thin living membrane in vitro. This membrane, the urinary bladder of the toad, consists of a single layer of mucosal cells supported by a thin layer of connective tissue, containing bundles of smooth muscle and covered on its contramucosal surface by serosa. Our interest in studying this tissue is that it is capable of performing at least two of the major functions of the mammalian renal tubule: (1)

* Received for publication November 17, 1960.
Presented in part at the Forty-first Annual Session of The American College of Physicians, San Francisco, April 4-8, 1960.
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† Supported by grants from the John A. Hartford Foundation, Inc., the United States Public Health Service (Grant H-2822), and the American Heart Association, Inc.
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§ Investigator, Howard Hughes Medical Institute.
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it actively reabsorbs sodium;[7] (2) the rate of net water reabsorption from the bladder is markedly accelerated by mammalian antidiuretic hormone.[8]

For in vitro studies, the bladder may be mounted as a membrane separating two halves of a lucite chamber. Ringer's solution of appropriate composition is introduced into each chamber half. The active sodium transport, from the mucosal (or urinary) side to the serosal (or body fluid) side is monitored electrically by the short-circuiting technic of Ussing and Zerahn;[9] under these conditions one obtains a continuous measurement of the net, or active, sodium transport.[7] Net water movement is directly determined gravimetrically as the change in weight of the Ringer's solution in the two chamber halves during the course of an experiment. Net water movement is expressed as microliters per square centimeter of tissue per hour, (μL./cm.^{2}/hr.) and results are accurate to approximately $\pm$ 3 microliters (μL.) per square centimeter per hour.

The osmolality of all solutions used was determined with a Fiske osmometer. A Baird flame photometer was employed in the determinations of potassium.

Results

1. *Sodium Transport and Water Movement Across the Isolated Toad Bladder:* It will be helpful to give a brief description of these two properties of the preparation before proceeding with the specific problems of this study. By application of the technics of Ussing and Zerahn[9] it has been demonstrated that the short-circuit current exactly equals the active reabsorption of sodium by this membrane.[7] Figure 1 shows that when mammalian neurohypophyseal hormone is added even in large amounts to the medium

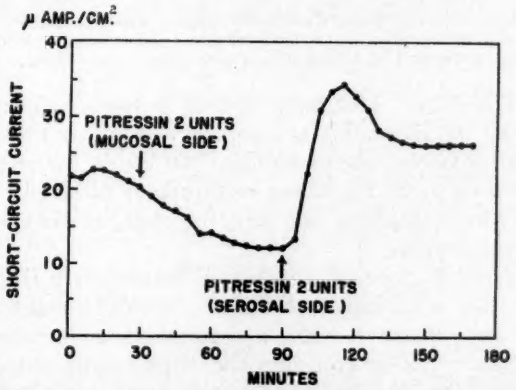

FIG. 1. Demonstration of the unilateral stimulatory effect of commercial vasopressin on short-circuit current (active sodium transport)[7, 10] in the isolated toad bladder. Note that even when a large amount of the hormone is added to the medium bathing the mucosal surface of the membrane no effect is discernible. The same quantity of the hormonal preparation added to the solution bathing the serosal side results in a prompt and large stimulation. (Figure reproduced from Leaf et al., J. Gen. Physiol. 41: 665, 1958.)

bathing the mucosal surface of the membrane, the short-circuit current is unaffected. Hormone added to the serosal surface, however, regularly produces a prompt and marked stimulation of short-circuit current, that is, of active sodium transport.[10]

In addition to this effect on active sodium transport, neurohypophyseal hormone exerts a profound effect on net water movement across the toad bladder. Prior to the addition of hormone, there is little net movement of water (2 to 10 μL./cm.^{2}/hr.) across the membrane, even when a large osmotic gradient is imposed by placing dilute Ringer's solution on the mucosal side, and isotonic Ringer's solution on the serosal side (Table 1A). Administration of hormone under these conditions results in large net water fluxes (Table 1B). The net water movement bears a linear relationship to the osmotic gradient, and may be very large in experiments employing large osmotic gradients across the membrane. In the absence of an osmotic gradient, the addition of hormone does not result in a significant net water

TABLE 1

Net and Unidirectional Fluxes of Water Across Isolated Toad Bladder With and Without an Osmotic Gradient and Without or With Vasopressin

Number Experiments	Gradient (mOsm./Kg. Water)	Mean Net Flux, Δ_v (μL./cm.^{2}/hr.)
A. Without Hormone		
5	0	−2*
6	160	5
B. With Hormone		
12	0	3
6	60	77
8	150	186
5	170	207

* The minus sign indicates measured net water transfer was in serosal to mucosal direction but the small value found is indistinguishable from zero. All other net movements were from mucosal to serosal surfaces and from higher to lower concentrations of water.

movement (Table 1B). This latter finding provides evidence that water movement across the membrane is a passive process, and does not involve active transport as in the case of sodium. Of course, in vivo, the osmotic gradient must arise from the active reabsorption of sodium by the renal tubule and bladder epithelium, and this, therefore, is the energy-requiring step in water reabsorption.

2. *The Reduced Response to Chronically Administered Hormone:* If exogenous vasopressin is administered daily to normal human subjects or to dogs, and the usual intake of water is maintained, a characteristic train of events takes place. For several days the urine remains concentrated, and as a consequence, the subject retains water, gains weight, and develops a marked dilution of body fluids with attendant hyponatremia.[11] After this initial three to 12 day period, however, there is a decrease in urine concentration and the subject may come into water balance again, despite the continued administration of vasopressin.[12-14]

TABLE 2

The Effect of Serosal Hypotonicity on the Net Movement of Water Following Vasopressin

Number Experiments	Gradient mOsm./Kg. Water	Tonicity of Serosal Medium mOsm./Kg. Water	Net Flux, Δ_w (μL./cm.^{2}/hr.)	S. M. Mean
11	57	219	80.1	±5.2
7	57	151	46.0	±7.2
	Difference		34.1	±8.7
	P		<.01	

In considering this phenomenon of escape from the action of vasopressin, Levinsky et al.[13] suggested that overhydration might directly affect the permeability properties of the renal tubular epithelium, and thereby might interfere with the action of the hormone. To assess the effect of dilution of body fluids per se on the ability of a simple cellular system to respond to hormone, we have measured water movement across the toad bladder under two experimental conditions. In the first, the serosal (or body fluid) side was bathed by the usual isotonic Ringer's solution, which, for the toad, is approximately 220 mOsm./Kg. of water. In the second set of experiments the serosal bathing medium was diluted to 69% of its isotonic value, and the mucosal medium was also made more dilute so that in both sets of experiments an identical osmotic gradient (or driving force) existed across the membrane. Table 2 shows that the net water movement in response to hormone was considerably less when the serosal medium was dilute. Dilution of the serosal bathing medium to an extent which may be encountered in water-intoxicated subjects does indeed decrease the net reabsorption of water induced by vasopressin.

3. *The Concentrating Defect of Potassium Depletion:* In potassium depletion of whatever etiology a concentrating defect may be seen which is resistant to exogenous vasopression.[15] It seemed of interest to determine whether a reduction in the concentration of potassium in the bathing medium affects net water movement across the toad bladder in response to vasopressin. Accordingly, water movement was determined at concentrations of potassium in the media of 3.5, 2.2, and 0.07 mEq./L. (Table 3). The mean figures show a small reduction in net water reabsorption (Δ_w) as the concentration of potassium was decreased. The differences, however, were

TABLE 3

Comparison of Net Flux of Water Across the Isolated Toad Bladder With and Without Potassium in the Medium

Medium K (mEq./L.)	Net Flux, Δ_w (μL./cm.^{2}/hr.)	Number Experiments
3.5	194 ± 10.5	5
2.2	186 ± 9.0	8
0.07	168 ± 10.4	12

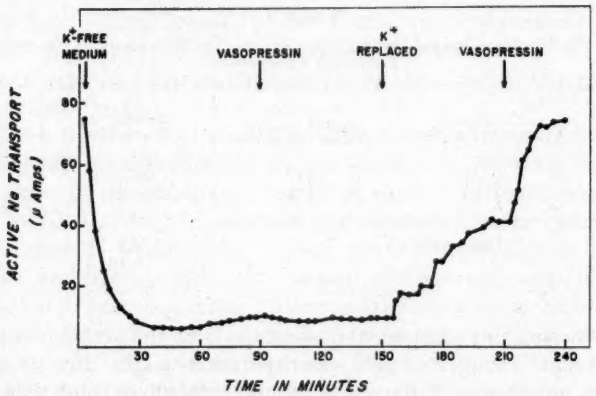

FIG. 2. The effect of removing potassium from the medium on active sodium transport by the isolated toad bladder. Note the rapid drop in transport when potassium is initially removed. Usually sodium transport declines to zero. In this state no stimulation is observed when vasopressin is added. The reversibility of this inhibition of sodium transport is indicated by its return upon addition of potassium to the medium. The stimulatory effect of vasopressin again becomes apparent.

small and not statistically significant in the number of experiments carried out at each concentration of potassium. Note that even in the medium essentially free of potassium, one observes almost the full hormonal effect on water movement.

In contrast to the negligible effect on the reabsorption of water, removal of potassium regularly produces a striking effect on active sodium transport. Figure 2 shows the rapid drop in short-circuit current, and hence active

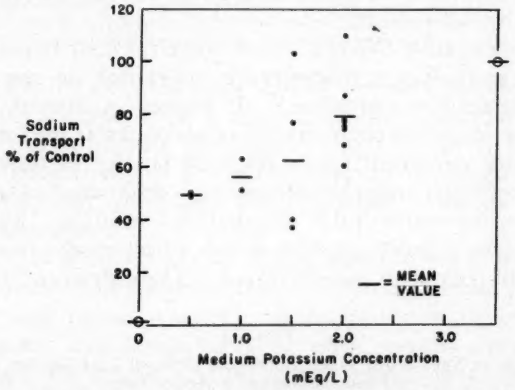

FIG. 3. Relationship of active sodium transport to concentration of potassium in the bathing medium. The 100% value at potassium concentrations of 3.5 mEq./L. of bathing medium and the value of essentially zero sodium transport in the absence of potassium in the medium are based on many observations. Although there is considerable scatter in individual values a graded reduction in sodium transport with concentrations of potassium between these extremes is evident.

sodium transport, when potassium-free Ringer's solution is used as the bathing medium.[16] In many experiments, active sodium transport ceases altogether. These effects are reversible as indicated by the resumption of sodium transport when potassium is returned to the medium.

Figure 3 shows that a graded reduction in active sodium transport occurs in response to a graded reduction in the concentration of potassium in the bathing medium. Here, the control short-circuit current was determined using Ringer's solution containing 3.5 mEq./L. of potassium. When a steady reading was obtained, the bathing medium was changed to one containing a lower potassium concentration (2, 1.5, 1, or 0.5 mEq./L.). The short-circuit current was again allowed to attain a steady value, and readings were taken over approximately a one-half hour period. The bathing medium was then changed back to the control solution, and the steady state current recorded. The entire procedure was then repeated, usually two or three times. There was a definite decrease in active sodium transport when the potassium in the medium was lowered; furthermore, the decrease was shown to be reversible, since the short-circuit current rose to close to its original value during the recovery periods.

Discussion

The acute experiments described above indicate that dilution of the serosal side of the isolated toad bladder significantly reduces net water movement in response to vasopressin. Reduced concentrations of potassium in the bathing medium, on the other hand, have little effect on net water movement, but prevent the active reabsorption of sodium. In the mammalian kidney interference with either the reabsorption of water in response to vasopressin, or with the active transport of sodium by the renal tubular epithelium could result in an inability to concentrate the urine. This may be better appreciated by a brief review of the present concept of the concentrating mechanism (Figure 4).

Some 85% of the glomerular filtrate is reabsorbed isotonically in the proximal tubule. The remaining fluid enters the loops of Henle and passes down into the medullary area, which is distinctly hypertonic.[17] Tubular urine as well as medullary fluid at the papillary tip approach the concentration of the final urine during antidiuresis.[3] Active sodium transport from tubular urine to interstitium must occur in the ascending limb of the loop of Henle since the urine returning to the cortex in the distal convoluted tubule is hypotonic.[2, 3] The cortical interstitial fluid is isotonic, reflecting the tonicity of the extracellular fluids in general.

During antidiuresis, antidiuretic hormone is thought to act in the distal convoluted tubule, where the hypotonic tubular urine is rendered isotonic by equilibration with the cortical interstitial fluid.[2, 3] It probably acts also in the collecting tubule, where the final act of concentration of the urine occurs as tubular urine equilibrates with the hypertonic medullary interstitial

fluid. Thus, the concentrating mechanism depends on both the effect of antidiuretic hormone on the permeability of the renal tubular epithelium to water, and on the active transport of sodium from tubule to medullary interstitial fluid which creates the gradient for water movement.

In Pitressin-induced water intoxication it is assumed that the cortical interstitial fluid becomes hypotonic, as does the extracellular fluid generally. Such a dilution might reduce the osmotic gradient across the distal convoluted tubules, thus resulting in a reduced reabsorption of water. In addition, there would be a direct interference with the response of tubular cells to antidiuretic hormone, as demonstrated in the toad bladder. Both con-

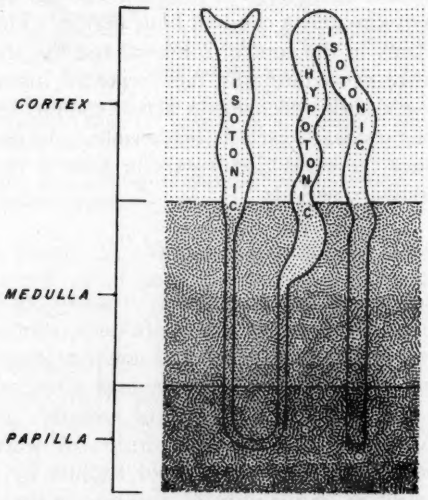

FIG. 4. Schematic representation of a nephron from the mammalian kidney to illustrate the main features of the renal concentrating mechanism. The cortex of the kidney is isotonic with extracellular fluids, while the concentrations in the medulla progressively increase toward the papilla, as indicated by the graded density of stippling. The concentrations in interstitial fluid, loop of Henle, and terminal collecting duct in the papilla are all high and, during antidiuresis, equal in osmolality to the final bladder urine.

ditions, therefore, would limit the reabsorption of water and lead to an escape from the antidiuretic action of vasopressin.

Just how dilution of the serosal bathing medium interferes with the action of the hormone is not clear. Evidence has been presented [18, 19] that, in the absence of vasopressin, the mucosal surface of the single cell layer is considerably less permeable than the serosal surface, and that the hormone acts by increasing the permeability of the mucosal surface. Therefore, it seems possible that dilution of the serosal medium might somehow prevent access of the hormone to its site of action at the mucosal cell membrane. Even though excessive quantities of hormone were used, a reduced response of sodium transport and of water reabsorption to hormone was seen. Dilu-

tion of sodium alone in the serosal medium cannot be responsible for the reduced effect of vasopressin since its complete absence does not have such a marked effect.[20] All constituents of the diluted Ringer's solution other than sodium and chloride were maintained at their usual concentrations. The escape from the hormonal action can therefore be described at the present only as a decreased cellular response to the action of the antidiuretic hormone. It is of interest in this regard that this self-limiting response at the receptor level should serve to protect the subject from further action of the hormone and from increasing water intoxication.

Huf [21] had previously observed an inhibitory effect of low medium potassium concentrations on active sodium transport by isolated frog skins. Ussing [22] refers to similar observations which are consistent with his hypothesis that sodium, actively transported across the serosal cell surface, is exchanged for potassium in the external medium.[23] Removal of potassium from the medium bathing the toad bladder had little effect on net water movement under the experimental conditions employed, but resulted in the complete cessation of active sodium transport. If potassium was not completely removed from the bath, but set at levels below 3.5 mEq./L., sodium transport was significantly reduced.

A comparable decrease in sodium transport by the mammalian renal tubule would, of course, reduce the solute concentration of the medullary interstitial fluid and thereby depress concentrating ability. A recent study by Manitius et al.[24] on chronically potassium-depleted rats and dogs suggests that this sequence of events does indeed take place. Sodium and total solute concentrations of renal papilla and medulla in these animals were lower than in normal controls. Balance studies showed a significant degree of salt-wasting in the animals depleted of potassium, constituting further evidence of interference with active sodium transport. The extent of impairment of water reabsorption could not be directly measured. That there was also some impairment in water reabsorption was suggested, however, by the fact that the reduction in urine concentration could not be wholly accounted for by a reduction in medullary solute concentration.

Conclusions

1. Experiments have been performed in vitro employing a living membrane to gain further understanding of the resistance to the antidiuretic effects of vasopressin encountered in two clinical situations.

2. In the escape from the effects of vasopressin administered chronically, dilution of the body fluids per se would appear to play the major role. This is supported in the experimental preparation in which the action of hormone is significantly reduced when the osmolality of the serosal medium is decreased.

3. In potassium depletion, failure to attain a highly concentrated medullary interstitial fluid because of interference with sodium reabsorption is

probably the most important factor in the associated vasopressin resistant polyuria. This is suggested in the in vitro studies by such an inhibitory effect of reduced concentrations of potassium in the medium on sodium transport with virtually no effect on the reabsorption of water.

4. It is emphasized that explanations obtained from a well-defined in vitro system, as has been employed in these studies, can only serve to indicate directions for further investigations in the actual clinical situations.

Summario in Interlingua

Studios in vitro esseva effectuate con un membrana vive pro ganiar un plus satisfacente comprension del resistentia contra le effectos antidiuretic de vasopressina que es incontrate in duo situationes clinic. Le vesica urinari del bufon esseva usate como instrumento de investigation, proque iste tissu es histologicamente simple e imita—con respecto al movimento de aqua e al responsa a hormon antidiuretic—le tubulos renal de mammales in importante punctos.

Le prime condition examinate esseva le escappamento ab le effectos de vasopressina que occurre durante le administration chronic del hormon. In iste situation, le dilution del liquidos del corpore per se pare haber un rolo major. Iste these esseva supportate in le preparato experimental per un grado significative de reduction in le action de vasopressina quando le osmolalitate del medio esseva reducite al latere ubi le membrana in vivo es exponite al liquido corporee.

Le secunde condition studiate esseva le non-occurrentia de alte concentrationes urinari in le presentia de un depletion de kalium. In iste situation, le phenomeno que un altemente concentrate liquido de interstitio medullari es prevenite a causa del interferentia in le reabsorption de natrium es probabilemente le plus importante factor in le associate polyuria resistente a vasopressina. Iste explication esseva supportate in le studios in vitro per un effecto inhibitori exercite in le transporto de natrium per reducite concentrationes de kalium in le medio, accompaniate de virtualmente nulle effecto in le reabsorption de aqua.

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DIFFERENTIAL DIAGNOSIS BETWEEN DIABETES INSIPIDUS AND COMPULSIVE POLYDIPSIA *

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Diabetes insipidus is defined as the disease in which antidiuretic hormone (ADH) is not produced even in the presence of an appropriate stimulus. As a result, the patient passes large volumes of a hypotonic urine. There is also the disease, nephrogenic diabetes insipidus, in which sufficient amounts of ADH are produced, but the collecting tubules of the nephrons are insensitive to its action. On the other hand, clinical disturbances have been described in which the hypothalamic center of thirst is persistently affected and thirst sensation disappears or increases.[1] In the case of hyperdipsia, the increased water intake inhibits the release of ADH and physiologic diabetes insipidus is brought on, even though the ability to produce ADH in the presence of an appropriate stimulus remains normal. Such alterations may coexist with primary diabetes insipidus,[2] the combination of diabetes insipidus with hypodipsia being particularly dangerous. There is still another entity described many years ago,[3] which consists in the abundant and prolonged water intake, with the same consequences, as far as ADH inhibition is concerned, as organic hyperdipsia; but this entity is not persistent nor does it seem to be due to any hypothalamic lesion. It has been called psychogenic, compulsive, or hysterical polydipsia. Due to this multiplicity of similar conditions, one is prone to use the term "diabetes insipidus syndrome." From a practical point of view it is important to differentiate psychogenic polydipsia from the other conditions, because it is susceptible to definitive correction and does not need perpetual treatment as does diabetes insipidus. Even though simple dehydration theoretically should make the diagnosis,[4] this is not so, generally because patients with compulsive polydipsia often respond as badly as do the patients with diabetes insipidus.[5] This is why a battery of tests has been developed to make the differential diagnosis. We have used the following in the series we now present: serum osmolarity,[5] dehydration,[4] intravenous administration of aqueous vasopressin and study of its effect on urine osmolarity,[4] combination of these last two procedures,[6] and administration of hypertonic saline,[7] nicotine,[8] and vasopressin in oil.[9]

* Received for publication August 22, 1960.

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Material and Methods

Four patients with polyuria and polydipsia were studied in whom differential diagnosis between diabetes insipidus and compulsive polydipsia was considered, other possible causes of the alteration being excluded (diabetes mellitus, chronic renal insufficiency, hyperparathyroidism, kaliopenic nephropathy, Fanconi's syndrome).[10]

On admission to the metabolic ward the patients received a diet constant in its components, except for water, which was allowed freely. Complete clinical history and pertinent determinations with the common laboratory methods were recorded in order to discover any of the above mentioned defects; intracranial disease was also investigated by means of radiology and electroencephalography. In the investigative laboratory, serum and urine osmolarity were measured by depression of the freezing point with a Fiske osmometer.*

The investigative procedure included the following steps:

1. Twelve-hour urine volume and osmolarity measurements through several days.

2. Dehydration. Dehydration was carried out until the patient had lost 3 to 5% of body weight, or until he was not able to proceed further without having water.

3. Study for localizing the lesion in the ADH system.[8] For this study the bladder was catheterized in order to collect urine every five to 10 minutes; two three-way stopcocks were adjusted in the antecubital veins. Thus the patient was hydrated intravenously with 2.5% glucose solution, 20 ml./Kg. of body weight, at 25 ml./min., with a constant infusion pump. The maximal diuresis curve was awaited; then, 0.25 to 3 mg. of a solution of pure nicotine † in distilled water was injected intravenously. Individual dose was regulated according to the hypothalamic effect, manifested by subjective symptoms and by urine volume. When maximal diuresis recurred, 15 to 100 mU. of aqueous vasopressin ‡ were injected intravenously. Until this moment hydration was maintained by replacing orally the water lost in diuresis and perspiration (1 ml./Kg. of body weight); after vasopressin administration, the recurrence of maximal diuresis was awaited. Then, without replacing water losses, in order to avoid both dilution of hypertonic saline and sudden hypervolemia, a 3% sodium chloride solution (10 ml./Kg. of body weight) was infused at the rate of 14 ml./min. with a constant infusion pump. The whole experiment was performed in one or several days.

4. The last step consisted in the administration of five units of vasopressin in oil,§ intramuscularly.

* Results are expressed in terms of osmolarity since the standard solutions were made up per unit volume.—Ed.

† Nicotine No. 1242, Eastman Organic Chemicals, Rochester, N. Y. Mol. wt. 162.23.

‡ Pitressin, Parke-Davis, aqueous solution, 10 units per ml.

§ Pitressin Tannate in Oil, Parke-Davis, 5 units per ml.

Osmolar and free water clearances [11] were used to interpret the results, on the basis that reduction in free water clearance indicates ADH effect, when there are no significant changes in glomerular filtration rate [12] or in renal solute excretion.[13]

Results

The results are presented in Tables 1 through 4 and in Figures 1 through 5. Graphs express urine volume per minute in the ordinates and time in the abscissae; osmolar clearance is indicated with slanted lines from the peak of urine volume downwards in such a way that the open column beneath it represents free water clearance. When osmolar clearance is equal to urine volume, the urine is isosmotic, and when osmolar clearance is larger and goes below the zero line, it implies tubular reabsorption of free water—the production of hyperosmotic urine.

Clinical Features: As is seen in Table 1, the outstanding clinical features are not of diagnostic value except for the regularity of symptoms in patients

Table 1

Clinical Data and Osmolarity of Serum and Urine at the Time of Admission

Patient	Sex	Age (Years)	Duration (Years)	Remission	Urine Volume L./24 Hrs.	Regularity of Symptoms	Onset	Osmolarity mOsm./L.	
								Serum	Urine
A.P.	F	35	2 (mos.)	No	8	Yes	Gradual	288	71
M.F.	M	22	10	No	7–9	Yes	Gradual	300	80
E.A.	F	20	5	No	6–8	No	Gradual	284	26
C.N.	F	32	5	No	8–10	No	Gradual	288	215

with diabetes insipidus. It is true that the patients having compulsive polydipsia (E.A., C.N.) had a clear-cut neurotic character (diagnosed as hysterical by the psychiatrist), but we have also seen some neurotic patients with diabetes insipidus, not included in this report. It may be of interest that both polydipsic patients claimed to have had polydipsia before polyuria; while this history may be unreliable, it is in accord with the observations of Weir et al.[14] It is also worth while to note that the only demonstrable intracranial disease was in E.A., who had a convulsive epileptiform syndrome, a calcified choroid plexus shown in the cranial roentgenologic film, and bilateral and synchronic discharges of deep origin in the electroencephalogram.

Dehydration: The results of the dehydration test can be seen in Table 2. Urine osmolarity after dehydration was high and not far from normal in one case of compulsive polydipsia (C.N.), which is of diagnostic value; it was "partial" in one patient with diabetes insipidus (M.F.) and in the other case of compulsive polydipsia (E.A.); it was negative in the other case of diabetes insipidus (A.P.). In other words, the procedure does not solve

TABLE 2
Results of the Dehydration Test

Patient	Duration (hours)	Weight Loss*	Urine Osmolarity		Serum Osmolarity	
			Before (mOsm./L.)	After (mOsm./L.)	Before (mOsm./L.)	After (mOsm./L.)
A.P.	12	4.3	18	245	288	303
M.F.	17	5.4	80	465	300	322
E.A.	16	—	26	437	—	—
C.N.	16.5	2.6	475	744	274	296

* Weight loss is expressed in per cent of the initial body weight.

the diagnostic problem and in the main is unable to differentiate between what can be termed "partial" diabetes insipidus and primary polydipsia.

In Table 2 there are two very low urine osmolarities (18 and 26 mOsm./L.). They certainly are excessively low, since most authors admit that the lowest found in man is around 50 mOsm./L., but they were checked and yielded the same result. Of course, we have no explanation for such findings.

Vasopressin Administration: Aqueous vasopressin by the intravenous route was administered at the end of the dehydration period in one patient (M.F.). The experiment was performed when the patient had lost 6.1% of initial body weight after 18 hours of dehydration; in that period serum osmolarity rose from 288 to 320 mOsm./L. and urine osmolarity from 75 to 340 mOsm./L.; at the end of that period, 100 mU. of aqueous Pitressin were administered intravenously and urine was collected every 10 minutes through a Foley catheter. In the next 55 minutes, urine osmolarity increased gradually from 385 to 492 mOsm./L.

Table 3 compares the urine osmolarity of patients after dehydration with that attained in the next 12 hours following the administration of 5 U. of

TABLE 3
Comparison of Urine Osmolarity After Dehydration, and in the 12 Hours Following Injection of Vasopressin in Oil

Patient	Urine Osmolarity (mOsm./L.)		
	Dehydration	Pitressin Tannate in Oil	
		First Injection	Subsequent Injections
A.P.	245	468	922
M.F.	465	540	586
			688
E.A.	437	158	430
			880
			1,084
C.N.	744	469	—

vasopressin in oil. It is apparent that in patients with diabetes insipidus, urine osmolarity is higher with vasopressin, while in those with compulsive polydipsia it is higher with dehydration. In patient E.A., and in both patients with diabetes insipidus (A.P. and M.F.), subsequent injections produced more concentrated urines than did the first injection. This agrees with the observation that high and prolonged water intake produces renal resistance to ADH action.[15, 16] Of course, we were certain that Pitressin had been adequately prepared and that the ampules belonged to the same batch which previously produced a maximal effect in the same patients and in others.

"Study for Localizing the Lesion in the ADH System": The results are summarized in Table 4. In order to judge these results decrease in free

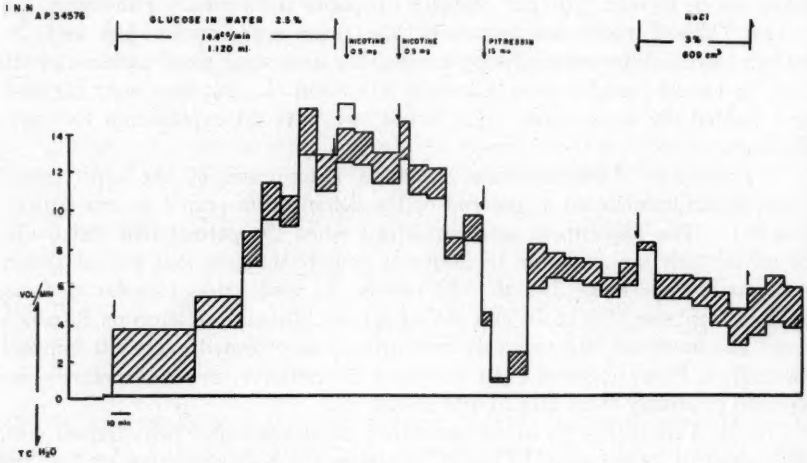

FIG. 1. Patient A.P. Diabetes insipidus with partial lesion of the hypothalamus.

water clearance is taken into account and expressed in terms of per cent of the initial value. Accordingly, a 100% response is obtained when urine becomes isosmotic, and a higher value than 100% when urine becomes hyperosmotic.

In A.P. (Figure 1) responses to nicotine, vasopressin, and hypertonic saline were in the 36, 91, and 53% range, respectively. These responses indicate a partial hypothalamic lesion.

In M.F. response to nicotine was 266%; immediately prior to nicotine administration, the patient sat on his bed for a moment, consequently, urine became nearly isosmotic. Perhaps this explains such a high response to nicotine. Response to vasopressin was 94%, and to hypertonic saline 33% with an increase in serum osmolarity of 19 mOsm./L., and a maximal serum level of 301 mOsm./L. Since response to dehydration was fairly good, with

TABLE 4

Tests for Localizing the Lesion in the ADH System

Patient	Hydration			Nicotine				Vasopressin				Hypertonic Saline				
					Response†				Response†			Response†				
	Volume ml./min.	Time min.*	CH_2O	Dose	Volume ml./min.	CH_2O	Time min.*	Dose mU.	Volume ml./min.	CH_2O	Time min.*	Volume ml./min.	CH_2O	Time min.*	Serum Osmolarity mOsm./L.
A.P.	15	0	12.7	0.5	12.8	11.3	35	15	9.5	8.3	15	6.9	5.8	0	296
					8.3	7.2			0.9	0.7		4.5	2.7		344
M.F.	9.8	65	8.4	0.5	2.8	0.03	25‡	100	6.2	5.3	25	7	6	30	282
					2.0	−0.05			2.6	0.3		5.4	4		301
M.F.												5	3	25	287
												7	0.8		318
E.A.	14.9	60	13.1	0.25	14.9	13.1	60	25	10.4	9.0	30	8.5	5.8	15	282
					6.8	5.8			0.5	0.4		3.4	−0.3		311
C.N.	22	50	18.2	0.5	21.0	19.1	131‡	15	28	23.5	17	9.6	8.5	115	272
					2.5	−2.3			4	−1.4		1.8	−1.4		285

* Time is recorded from the end of the stimulus until the response occurs, and it is expressed in minutes.
† The figures in the column of responses are the values before stimulus (upper one) and after it (inferior one).
‡ See text.

serum osmolarity increase of 22 and maximal serum level of 322 mOsm./L., the test was repeated, infusing the same amount of 3% sodium chloride solution but at a faster rate (25 ml./min.). With this procedure the change in serum osmolarity was 31 mOsm./L. and the maximal level attained was 318 mOsm./L.; free water clearance decreased by 126% of the initial value. Accordingly, all three stimuli produced a normal response.

In E.A., responses to nicotine and vasopressin and to hypertonic saline were in the 56, 96, and 105% range, respectively. Thus, with nicotine, no more than a partial response was obtained, indicating a hypothalamic lesion; this localization is not in accord with the good response obtained with hypertonic saline.

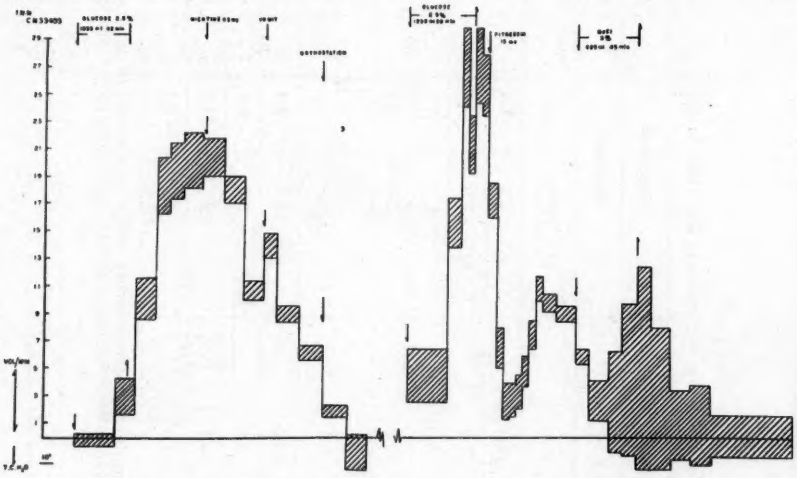

FIG. 2. Patient C.N. Compulsive polydipsia. Test for localizing the lesions in the ADH system.

In C.N. (Figure 2), responses to nicotine, vasopressin, and hypertonic saline were in the 112, 94, and 116% range, respectively. Thus every part of the ADH system appears normal in this case. It must be stressed that orthostatism and vomiting occurred (with nicotine injection) acting as additional and probably significant stimuli.

Attention should be called to the fact that orthostatism, even if only momentary, results in a diminution of free water clearance since it is known to stimulate ADH,[17] as shown in two of our patients (M.F. and C.N.).

Comment: Administration of vasopressin in oil produced slight symptoms of water intoxication in A.P. and E.A., one classified as diabetic insipidus and the other as compulsive polydipsia. This is not in accord with other authors [4, 9, 18] who find that vasopressin in oil only produces water intoxication in polydipsic patients; they believe that this phenomenon has

diagnostic value. Thorn and Stein [19] also report signs of water intoxication in patients with diabetes insipidus so treated. This seems only natural since polydipsia, regardless of its origin, finally becomes a habit and persists even if polyuria is suppressed. In patient C.N. (Figure 3) the injection of one single Pitressin tannate in oil ampule (5 U), together with superficial psychotherapy, produced complete alleviation of symptoms, and she voided hypertonic urine in normal volume during several months. Afterwards, this patient suffered an intense emotional shock and started to pass abundant volumes (3 to 3.5 L./24 hrs.) of hypotonic urine (270 and 44 mOsm./L.). After she had voided repeatedly she was intensely thirsty; following our advice she restricted her fluid intake to 1.5 liters a day, and had clinical signs of moderate dehydration. Nevertheless, hypotonic polyuria persisted for three days and finally it became normal again. This situation recurred

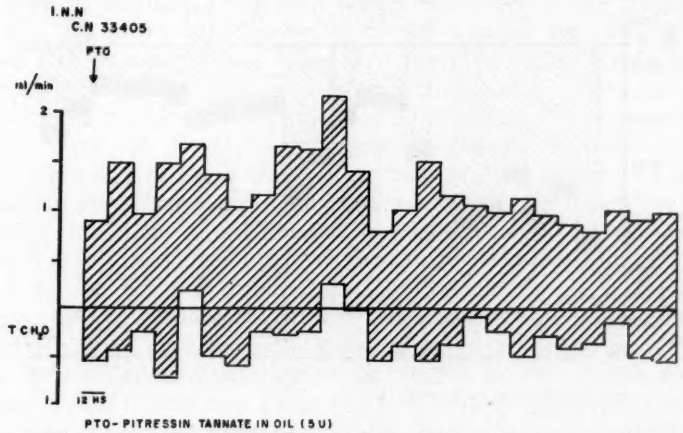

FIG. 3. Patient C.N. Compulsive polydipsia. Osmolar clearance in 12-hour period, following injection of one dose (5 U.) of vasopressin in oil.

exactly in the same way as a consequence of family trouble that brought about anxiety.

In patient E.A., clinical history and some of the tests performed led to the probable diagnosis of compulsive polydipsia; yet, diabetes insipidus could not possibly be ruled out because of the presence of a convulsive epileptiform syndrome, of electroencephalographic and roentgenologic alterations. On admission the patient received Pitressin in oil and was asked to refrain from drinking; in spite of no excess in water intake, once the pharmacologic effect of vasopressin was over, polyuria recurred continually; occasionally she had moderate clinical manifestations of dehydration, with negative water balance, yet the urine was persistently hypo-osmotic (Figure 4). After she had several doses of vasopressin in oil, and after several days in water balance, a placebo was given to her. As can be seen in the graph, this procedure was

useless. She was discharged with the diagnosis of diabetes insipidus and she came regularly to the hospital to receive shots of Pitressin tannate in oil. The duration of its effect was very variable; when her psychologic condition was easier, it lasted for as long as 20 days. Vasopressin was then replaced by a placebo (thiamine) and the effect was identical. During those periods of well being, obviously free of any exogenous antidiuretic factor, her urine volume was normal, she did not complain of thirst (daily water intake of one liter), and urine was amber in color. When emotional strain recurred, thirst and polyuria with colorless urine returned. Unfortunately we could not examine any of those colored urines, but it seems certain that the patient did not have diabetes insipidus, but compulsive polydipsia.

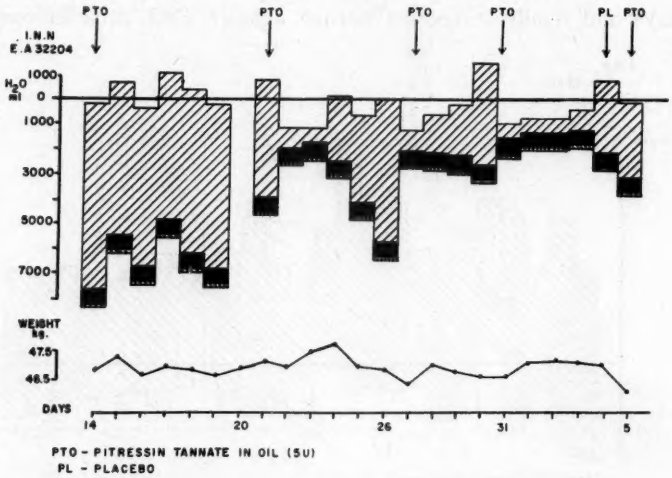

FIG. 4. Patient E.A. Compulsive polydipsia. Water balance plotted with the system of Reifenstein, Allbright, and Wells.[30] Intake is plotted from the zero line downwards, and the losses are plotted upwards from the bottom of the intake. When losses reach the zero line, equilibrium is attained; when they do not reach it, there is positive balance; when they pass the zero line, there is negative balance.

Patient M. F. also received Pitressin tannate in oil frequently enough to keep him free of polyuria and polydipsia for 21 days. Between 36 and 48 hours after the drug was injected, urine became hypotonic and thirst and polyuria recurred. After that period, Pitressin was substituted by placebo for several days, but polyuria and polydipsia recurred as intense as before, which supports the diagnosis of diabetes insipidus. Finally, the patient was once again subjected to dehydration, losing 6.1% of body weight in 18 hours; serum osmolarity increased from 291 to 308 mOsm./L., and urine osmolarity from 77 to 144 mOsm./L. When 100 mU. of aqueous vasopressin were administered intravenously, immediately after dehydration, urine osmolarity increased to 391 mOsm./L.

Discussion

As stated before, clinical data are of little help in the differential diagnosis between idiopathic diabetes insipidus and compulsive polydipsia. In our cases we find the neurotic character, polydipsia preceding polyuria, and irregularity in the course of symptoms, present in polydipsic patients and absent in diabetic ones, to be the best clinical clues for diagnosis. Yet we have seen patients (not included in this series) with idiopathic diabetes insipidus having the same type of psychologic alterations and having an irregular course not dependent on anterior pituitary insufficiency [20] or diminished solute intake.[21]

Among the functional tests, the one that consists of administering vasopressin immediately following a period of dehydration should be especially mentioned because of its physiologic basis. Dehydration is said to be efficient when it produces loss of body weight of between 3 and 5%; then it seems to be the most powerful stimulus for ADH release.[10] There is ample evidence that in patients with compulsive water drinking insufficient responses to hydropenia are due to tubular resistance of the kidney to ADH action,[15, 16] and that these patients have the organic ability to produce that hormone. It is also known that maximal antidiuresis is obtained with a given amount of ADH and that higher doses prolong antidiuresis but do not intensify it.[22] Accordingly, when a person who is able to produce ADH is dehydrated, hydropenia will cause all its possible effect in accordance with the sensitivity of the kidney tubule to vasopressin, and exogenous Pitressin will not further enhance antidiuresis. This should be the case in compulsive polydipsia. When, on account of disease, hydropenia does not promote ADH release, exogenous vasopressin is free to act on the renal tubules and to increase urine osmolarity. Such should be the case in diabetes insipidus. Thus far, the test has proved reliable in the cases here presented and in some others, but theoretically there may be some exceptions, first, in patients with nephrogenic diabetes insipidus. Second, since it is assumed that renal tubular resistance to ADH is due to excessive and prolonged water drinking in psychogenic patients, it is very likely that untreated patients with diabetes insipidus have the same trouble because they also drink excessively and continually. As a matter of fact, this situation has been described [4] and it occurs in the patients to whom Pitressin tannate in oil was administered repeatedly (Table 3). Third, there may be patients with primary polydipsia in whom the hypothalamus is impaired and ADH is not produced. Comparison between urine concentration obtained with dehydration and with vasopressin, even if the tests are not done one after the other, has the same physiologic significance. Our results and, in general, those of Barlow and de Wardener [5] agree with the theoretical hypothesis. Accordingly, the test seems to be truly useful for differential diagnosis.

Regarding the test for localizing the lesion in the ADH system there are

several difficulties, as shown by our results. In the first place there must be, for accuracy's sake, a very careful technic, with attendant discomfort for the patient on whom it is performed. Then, in addition to the experimental stimuli, other nonspecific stimuli undoubtedly modify the results to a certain degree.[23] Besides, it is difficult to know which stimulus is excessive and which is just sufficient to produce a normal response in an organ partially impaired. There also are doubts regarding the quality of the response. Insufficient numbers of normal controls make it difficult to recognize accurately a normal response from an abnormal one. We believe that reduction in free water clearance, expressed as per cent of the value prior to the stimulus, is the best way of judging a response. This belief is based upon the knowledge that when glomerular filtration and solute excretion are maintained constant, free water clearance can only be modified by the circulating level of ADH.[13, 22] Rather than state that the response to a certain stimulus is normal, we prefer to compare the results with all three stimuli and to qualify as a poor response the slightest one, when there is an important difference between them. We think this is valid because nearly always diabetes insipidus is partial, and the degree of response varies with the dose of the stimulus.

The influence of the dose is beyond doubt, as mentioned and demonstrated by Lauson.[22] It is probable that quantitative differences in the stimuli explain the responses obtained in patient A.P.; the worst result was obtained with nicotine, which localizes the lesion to the hypothalamus. In such a case, the stimulus received in the osmoreceptor should not be effective; yet responses to dehydration and hypertonic saline were better, although abnormal, because the stimuli were more powerful than 0.5 mg. of nicotine. The case of E.A. is even more demonstrative. The intravenous administration of 0.25 mg. of pure nicotine produced symptoms of "hypothalamic stimulation," but antidiuresis was scanty. The patient had compulsive polydipsia and, since responses to dehydration and hypertonic saline were medium and satisfactory respectively, it is almost certain that the poor response to nicotine was due to insufficient dosage. Accordingly, in order to achieve a truly useful test for localizing the lesion, maximal or equivalent stimuli should be used in irritating each part of the system. A maximal dose of vasopressin is known to be 50 mU., as shown by Lauson [22] and by Orloff et al.[24]

The use of nicotine to stimulate the production of ADH is quite problematic. Burn, Truelove, and Burn [25] demonstrated that the same dose of nicotine has variable effects in different normal persons. Furthermore, Burn and Grewald [26] found that the effect of nicotine also varies at different moments in the same individual; this also happened in the patients of Dingman et al.[8]

The unpleasant symptoms produced by nicotine prevent the use of a dose large enough to make certain that it is maximal. Furthermore, the lack of a sure index of the efficiency of a certain dose in a particular individual

makes the problem more difficult. It has been demonstrated that antidiuresis can be obtained without symptoms of "hypothalamic intoxication." [25, 27] This indicates that the thresholds for subjective vagal symptoms and for ADH production are different, and therefore the possibility exists that a certain dose would be sufficient to produce symptoms of "intoxication," but not to attain the threshold for antidiuresis. In fact, the observations of Taylor and Walker [27] and of some others quoted by them indicate the presence in normal men of typical subjective manifestations provoked by nicotine, without any modification in water diuresis.

Accordingly, the nicotine test seems less reliable, and, by all means, the most difficult to control and, therefore, to interpret. It is likely that the resistance to nicotine that has been found to be characteristic of psychogenic polydipsia is nothing more than a matter of dosage and variation in sensitivity, of the same kind that is encountered in normal individuals.

The problem is similar with hypertonic saline. A given amount produces different effects according to the individual sensitivity, the previous degree of hydration, and the infusion rate. Whether the stimulus was sufficient or not can only be known afterwards when serum osmolarity is determined; even then it is difficult to assess whether the efficiency depends on the change or on the maximal osmolarity attained. From our results, the change seems to be more important, since in C.N. a satisfactory response with a change of plus 13 was observed in spite of a maximal osmolarity of 285 mOsm./L. In the other two patients in whom responses were positive (E.A. and M.F., second test), a great change occurred, but these patients also had high maximal osmolarity. In the first study M.F. had no response though serum osmolarity change and maximal value were higher than in C.N. (Table 4); of course, this can easily be explained because M.F. had diabetes insipidus and C.N. compulsive polydipsia. The response of M.F. on the second experiment can be attributed to the unusual intensity of the stimulus. Figure 5 shows graphically the influence of dosage on the response to hypertonic saline.

M.F. suffered from diabetes insipidus even though no macroscopic lesion was demonstrated that could explain the disease. The difficulty seemed to be found in the osmoreceptors, and was abolished when serum osmolarity increased beyond 318 mOsm./L.; this observation suggests that in this patient the threshold of response of the osmoreceptors was unduly high. Therefore, since the serum osmolarity needed to stimulate them is attained only in severe dehydration, in ordinary conditions ADH is not produced and the clinical picture of diabetes insipidus ensues.

In summary, it can be said that the test for localizing the lesion is useful and indicates fairly accurately whether or not the ADH system is normal when the appropriate stimuli are employed.

On the whole, the problem of differentiating between diabetes insipidus and compulsive water drinking turns out to be rather difficult. It is gen-

erally admitted that in diabetes insipidus there is an organic disease which prevents the production of ADH, even by unphysiologic stimuli under conditions of stimulation other than physiologic. Nevertheless, in a large number of cases no such organic cause is encountered. On the other hand, there are some patients in whom ADH production can be attained when strong stimuli are used, as in the case of M.F. In diabetes insipidus patients there is also a functional factor due to tubular resistance to vasopressin, probably produced by the high and prolonged water intake, which aggravates the intensity of symptoms and is susceptible to remission.[28]

On the other hand, most patients with compulsive polydipsia respond abnormally to the stimuli of ADH production. The reason for this seems

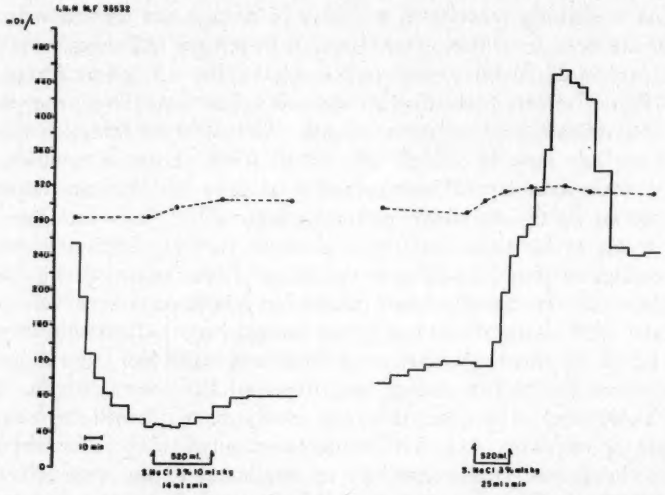

FIG. 5. Patient M.F. Diabetes insipidus. Continuous line indicates urine osmolarity and the broken line indicates serum osmolarity in the two experiments with hypertonic saline. To the left, it can be seen that urine remained hypotonic when serum osmolarity increased from 282 to 301 mOsm./L. during the saline infusion. To the right, urine concentration increased and became hypertonic to serum when serum osmolarity increased from 287 to 318 mOsm./L.

to be found in the above mentioned tubular resistance to vasopressin, but this does not explain either the origin of polydipsia or the frequent relapses and other features of the disease. The case of C.N., who complained of abundant diuresis before polydipsia and presented hypotonic urine even though she kept herself from drinking when she was under emotional strain, suggests ADH inhibition surely unrelated to overhydration. It is a known fact that emotions can inhibit ADH production momentarily, but the persistent situation in this case suggests a labile hypothalamic hypophyseal system apparently unrelated to a lesion of the thirst center.

De Wardener [29] had a similar experience with a polydipsic patient he treated with prolonged narcosis. His experiment also suggests ADH inhibition independent of water ingestion. It appears that the narcotic suppressed some active inhibitory mechanism that prevented ADH production during wakefulness.

It is clear that diabetes insipidus and compulsive water drinking are closely related. In fact, it can be said that, at least in some cases, compulsive polydipsia is nothing more than diabetes insipidus in the strict meaning of the word, with the difference that it is reversible. The possibility of reversibility makes the question of differential diagnosis important. Thus far, we have found that the best means of differentiating is through the administration of Pitressin after a period of dehydration. Another good way is to prevent the patient from drinking abundantly for 15 days at least, whether voluntarily or with the aid of vasopressin in oil, hypnosis, or narcosis. If vasopressin is used at the end of the therapeutic period it can be replaced by a placebo, or the patient can be asked not to drink more water than the amount considered strictly necessary. Otherwise, the comparison should be made of the patient's concentrating capacity during dehydration before and after vasopressin therapy. The patient with diabetes insipidus will remain unable to concentrate urine without exogenous vasopressin, the patient with primary polydipsia will develop a practically normal antidiuresis as the result of the hydropenia.

Summary

Four patients with polyuria and polydipsia were studied in order to make a differential diagnosis between diabetes insipidus and primary functional polydipsia. Several of the tests recommended for such cases were performed and the results were analyzed critically. It was concluded that the most definitive test consists of administering vasopressin intravenously immediately after a period of dehydration. If the Pitressin produces a more concentrated urine than the dehydration, diabetes insipidus is diagnosed; if not, compulsive polydipsia is diagnosed. It is felt that diabetes insipidus and psychogenic polydipsia are related in many ways, but that they differ in prognosis; hence it is important to differentiate between them.

Summario in Interlingua

Quatro patientes con polyuria e polydipsia esseva studiate pro establir un diagnose differential inter diabete insipide e primari polydipsia functional. Plures del tests recommendate pro tal casos esseva executate, e le resultatos esseva analysate criticamente.

Le technicas usate in le investigation includeva le sequentes: (a) Mesurationes de volumines urinari de dece-duo horas, con determination del osmolaritate durante plure dies. (b) Dishydratation usque le patiente habeva perdite inter 3 e 5 pro cento del peso corporee. (c) Studio pro localisar le lesion in le systema de hormon

antidiuretic. (d) Le administration de cinque unitates de vasopressina in oleo per via intramuscular.

Esseva concludite que le test le plus definitive consiste in le administration de vasopressina per via intravenose immediatemente post un periodo de dishydration. Si le pitressina produce un plus concentrate urina que le dishydratation, le diagnose es diabete insipide; alteremente, polydipsia compulsive es diagnosticate. Es opinate que diabete insipide e polydipsia psychogene es interrelationate in multe manieras sed que illos differe in le prognose. Ergo le differentiation inter le duo remane importante.

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THE CONSERVATIVE MANAGEMENT OF BARBITURATE INTOXICATION: EXPERIENCE WITH 95 UNCONSCIOUS PATIENTS *

By MATTHEW J. FERGUSON, M.D., and WILLIAM J. GRACE, M.D., F.A.C.P., *New York, N. Y.*

THIS paper reports our experience with the management of barbiturate intoxication in 140 patients over a six-year period (1953 to 1959). The patients were seen at St. Vincent's Hospital in the heart of Greenwich Village, New York, where there is an unusually high incidence of barbiturate overdosage. Only those patients who were unconscious or whose sensorium was depressed were admitted to the hospital, and only those who were hospitalized were studied.

Forty-five of the 140 cases were omitted from this report because they presented no therapeutic problem (Class 0 of Reed et al.[1]); because there was a question of whether barbiturates alone produced the coma or whether narcotics, bromides, tranquilizers, et cetera could be incriminated; or because hysteria was suspected as adding to the picture of apparent coma. There was no incidence of morbidity or mortality in this excluded group.

This report, therefore, deals with the remaining 95 patients who were unconscious due to barbiturate intoxication. Our analysis leads us to conclude that the analeptic management of barbiturate intoxication should be abandoned in the modern hospital, and that the physiologic method of treatment provides results far superior to those reported by the advocates of stimulatory drugs.

CLASSIFICATION

All cases were classified according to the scheme of Reed et al., based on the classic stages of anesthesia (Table 1). Although the difference

TABLE 1

Class	I	II	III	IV	Total
No. Pts.	45	13	21	16	95

between Classes II and III may have little significance, no attempt was made to alter the criteria. This plan of classification is simple and basically

* Received for publication October 13, 1959.

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sound, and should be strictly adhered to if various groups wish to compare with validity the results of their methods of therapy.

Classification according to Reed et al.:

Class 0: Asleep, but can be aroused and can answer questions.
Class I: Comatose, will withdraw from painful stimuli, reflexes intact.
Class II: Comatose, will not withdraw from painful stimuli, reflexes intact.
Class III: Comatose, reflexes absent, no depression of respiration or of circulation.
Class IV: Comatose, reflexes absent, respiratory depression or circulatory failure, or both.

Class 0 patients have been excluded from this study because they presented no therapeutic challenge. Patients were classified into the deepest class of coma observed while in the hospital. Only four patients progressed to a deeper state of coma after initial observation in the emergency room. Thirty patients were unconscious for undetermined periods of time before admission, and there is no doubt that some of these were in more profound

TABLE 2

Class	I	II	III	IV
Average age	36 yrs.	30 yrs.	44 yrs.	41 yrs.
Range	4–81	21–50	20–79	20–60

states of unconsciousness prior to entering the hospital. Where there was a question as to depth of coma, the patient was placed in the lighter class. Response to painful stimuli frequently placed a seemingly Class III patient into Class I.

Sex and Age: There were 37 males and 58 females. This male to female ratio differs from other large groups studied in that the female fraction is less. There would, however, have been a substantial increase in the number of females if the Class 0 cases had not been omitted.

The ages of patients ranged from four years to 81 years (Table 2). There were two children, ages four and nine. There were seven patients older than 60 years. Fifty-seven per cent were between 20 and 39 years. It is interesting to note that the patients in the more severe states of coma were in the older age groups.

Type of Barbiturate and Amount Taken: In only 60 cases was the exact name of the barbiturate noted; in the other 35 cases either there was no identification other than "barbiturates" or more than one type was mentioned in the notes. It was disappointing to be unable to document the exact amount of barbiturate taken. This information was recorded in only 49 cases, and in many of these there was no notation made as to the weight

of the individual capsules. Some patients denied barbiturate ingestion, but the drug was isolated from their urine, blood, or gastric washings.

A rough correlation was found between the class of the coma and the amount of barbiturate taken. For example, only one patient in Class IV had taken fewer than 20 capsules. In the latter part of this study a more concerted effort was made to determine the exact drug and the quantity of it taken. Surprisingly, the results were still discouraging. Some patients could only guess at the amount or were not sure of the individual capsule weight, and others knew only that the tablets were sleeping pills or barbiturates. Most striking were those patients who freely admitted suicidal intent yet were extremely reticent about giving the name of the drug or the amount taken. It appeared that this evasiveness was an attempt to protect or to conceal the source of the medication.

Length and Depth of Coma: The exact length of coma was known in 65 cases. In the other 30 cases the patients were unconscious for unknown periods of time prior to admission. In these cases the coma was measured

TABLE 3
Duration of Coma in Hours

Class	I	II	III	IV
Duration of known coma in 65 pts.	11	12	26	37
Minimal length of coma in pts. found unconscious	11+	16+	25+	38+
Range	1–53	7–42	4–96	17–84

from the time they were found unconscious. Inexplicably, these latter patients had an average length of coma which was greater than that of patients in whom the exact duration was known. Coma was considered terminated when the patients responded to verbal stimuli, sat up, or showed signs of recognizing their surroundings. Many fell back into a deep but arousable sleep after initial awakening. Table 3 indicates the average length in hours of known and unknown comas, and their range.

In Class I, the duration of coma in nine cases was under five hours and in 21 cases it was over 10 hours. In Class II, 10 of 13 cases had a duration of 10 hours, and three of these were over 30 hours. In Class III, all cases of coma except one lasted more than 12 hours. In Class IV, only two cases were of less than 24 hours' duration.

In general, there seems to be a good correlation between the class (depth) of coma and its length.

TREATMENT

This review was originally undertaken to gather data on all types of therapy at this hospital. However, it developed that virtually all cases of

barbiturate intoxication were managed by the so-called physiologic method. It is remarkable that over 50 physicians chose this type of therapy even though the Department of Medicine had not recommended any particular method during this time.

Analeptics: Forty-two cases received stimulants. However, 33 of these received only one or two doses of caffeine or benzedrine in the emergency room. After admission to the inpatient service these patients received no further stimulatory therapy. Needless to say medication mentioned did not terminate coma in any case.

Eight patients received caffeine on a two-, four-, or six-hour basis. Only one patient received vigorous analeptic therapy in pharmacologically effective doses. This was a 50-year-old woman (Class IV) who received amphetamine (benzedrine), 20 mg. every half hour, until she awoke after 40 hours. Consequently, for all intents and purposes, 94 cases were treated conservatively.

Gastric Lavage: Eighty of these patients (84%) received gastric lavage while in the emergency room. This procedure was not without complications. Five patients aspirated fluid during lavage; two of these developed apnea and they needed tracheostomy. Both of these were Class II patients. In another two patients (Class I and Class II), peripheral vascular collapse developed after lavage, which required treatment with vasopressor agents. The trachea was not intubated before lavage as some authors have recommended, nor, apparently, was any attention paid to the length of unconsciousness before lavage.

Intubation and Tracheostomy: Twelve patients had tracheal intubation; half of these patients required artificial respiration with Neuphor and Bennet machines. The vast majority of patients had a simple oral airway tube inserted. Half of the entire group received oxygen. Tracheostomy was performed in four patients. In two this was done because of aspiration and apnea following lavage, and in another it was done in the emergency room because of difficulty with intubating (this case later died). The fourth tracheostomy was done electively after 48 hours because of difficulty in keeping the airway clear. This patient awoke after 96 hours.

Vasopressor Drugs and Intravenous Fluids: Vasopressor drugs were used in 18 cases, and in these neosynephrine was used in all but two. Norepinephrine was the other agent used. These drugs were consistently effective in maintaining blood pressure for as long as 48 hours. Parenteral fluids were administered in 76% of this series.

Antibiotics: Antibiotics were used in 61%; all patients but one of Classes III and IV received them. Less than half of the patients in the first two classes were given antibiotics. In the later years of this study there was a notable tendency to withhold antibiotics in the first two categories, especially before 12 hours of coma had elapsed. Penicillin and the tetracyclines were most commonly used. It should be noted that pneumonia

developed in two patients who received antibiotics, and that febrile reactions occurred in 12 others despite antibiotic therapy.

General Medical Care: Careful nursing care was consistently used in all cases. All of the Class III and Class IV patients had special nursing attention. The nursing care consisted of (1) frequent changes of position every hour or two hours, (2) recording of vital signs every 15 minutes to one hour, (3) attention to pulmonary secretions, (4) careful recording of fluid intake and output, and (5) care of the eyes, skin, and mouth. Inasmuch as no special medications except vasopressor drugs were given, it is felt that the excellent nursing care played an outstanding part in the successful management of these patients.

Complications: Complications included at least five instances of aspiration and two of vasomotor collapse during gastric lavage. Another episode of aspiration and atelectasis followed an attempted tracheal intubation. There were four patients with pneumonia. Two of these developed pneumonia while receiving antibiotics; one had pneumonia on admission and another developed it while he was not on antibiotics. The following complications were also noted: brachial nerve neuritis, decubiti, broken teeth following intubation, phlebitis due to needle puncture, and hemorrhage from the tracheostomy site.

Mortality: There was one death among the 95 comatose patients.

A 34-year-old white male was found unconscious in his room after taking an unknown amount of secobarbital sodium (Seconal) and was brought to the hospital. On arrival in the emergency room his blood pressure was 60/0 mm. Hg; pulse, 108; respirations, four to five per minute and shallow. The pupils were dilated and nonreactive. Reflexes could not be elicited. The patient was lavaged and vasopressor drugs were started. An endotracheal tube was inserted. At this point, it was noted that the left lung was not aerating. A tracheostomy was done and it was then discovered that the endotracheal tube had become fixed in a main stem bronchus. The patient was placed on a Bennet artificial respirator. His vital signs remained stable. After 30 hours in the hospital, he awoke and spoke. However, six hours later he died suddenly. Permission for autopsy was refused.

Discussion

The basic problem in comparing the results of different methods of therapy in cases of barbiturate intoxication is the failure of the clinicians to use similar classifications. Unless there be concerted efforts to classify patient material accurately, comparisons of the statistics reported from the various clinics are not valid. In this series we have adhered strictly to the classification of Reed et al.[1]

This report adds more weight to the overwhelming evidence against the value of *stimulatory treatment.* On the basis of accumulated evidence it would seem that there is no place for analeptic therapy in a modern, well-equipped hospital. Vasopressor drugs and mechanical respirators obviate the use of analeptic drugs. Significantly, in this study arrhythmias, tachy-

cardias,[1] convulsions, nausea, vomiting, and postcoma psychosis,[2] which are frequently noted with analeptic therapy, did not occur. The problem of whether or not analeptic therapy should be used has been discussed by others, and the reader is referred to the work of Nilsson,[3] Kopanyi,[4] Ekenhoff and Dam,[5] Lavenson et al.,[6] and Plum and Swanson.[7] Shaw et al.[8] reported what appeared to be a superior antidote, Megimide (beta-ethyl-beta-methylglutarimide). However, later experience with this agent has not shown it to be significantly more effective than are the older drugs.[9]

While the results reported here are good, analysis of the records suggests that gastric lavage was done indiscriminately in this series. This procedure was not without its complications. Harstad et al.[10] were first to question its value, and their studies showed that if lavage is done four hours or more after the drug had been taken only insignificant amounts of barbiturate could be removed. Wright[11] confirmed this finding. The Copenhagen Center for the Treatment of Poisoning, which deals with about 800 cases of barbiturate intoxication yearly, abandoned lavage entirely when it was demonstrated that only small quantities of barbiturate (up to 100 mg.) could be aspirated.[12] If each case is considered separately with regard to the amount of drug taken, the length of time elapsed since ingestion, and the presence of gag reflexes, certainly lavage would be performed less often.

Although antibiotic prophylaxis was used in 61% of the patients in this series, it did not prevent pneumonia from developing in two patients and febrile reactions in others. This has been the experience of Petersdorf et al.[13] in their study of antibiotic prophylaxis in the unconscious, and of Weinstein[14] in his study of paralytic polio. With this evidence in mind it seems wise to withhold antibiotics unless some specific indication for their use arises, and then bacterial identification and sensitivity studies should be done before choosing an antibiotic. Another hazard, although remote, is the possibility of drug sensitivity in a patient who is unable to give a history.

The use of artificial respirators was necessary for those with depressed respiratory function. The Bennet respirator was used effectively here and is recommended, since it allows for more adequate nursing care than does the Drinker type. Airways were used in most of the patients and tracheal intubation with frequent replacement was used successfully in the more severely depressed patients. One elective tracheostomy was done. It seems unwarranted to make any set rule about tracheostomy after coma of 24, 48, or 72 hours' duration. Each case must be evaluated individually.

Peripheral vascular collapse responded quickly to neosynephrine and to norepinephrine. Blood pressure was maintained by these agents for as long as 48 hours. Attention to the cardiovascular system and to the maintenance of adequate blood pressure must be constant, since shock may lead to serious renal and cerebral difficulties. Intravenous fluids were given generously and attention was given to intake and output.

A most important modality of treatment in this series was good nursing

care, which consisted of meticulous attention to vital signs, positioning of patients, clearance of airway, and attention to care of eyes, skin, and mouth. One cannot overemphasize the importance of constant attendance by professional personnel in Class III and Class IV patients.

Unfortunately, it is not possible to compare the results of this group of patients with many of the large series previously reported. This is due to the inadequacy of defined criteria for classification of the depth of coma. The system used here is simple and if strictly adhered to in future reports would provide an accurate basis for comparison of the various therapeutic measures. It should be noted that this is not a padded schema, especially since Class 0 patients are excluded from it.

The mortality rate reported here is lower than that reported by the writers using this schema[1, 6] or that reported by groups using less well-defined criteria.

Summary

Ninety-four of 95 cases of barbiturate intoxication were managed without recourse to special stimulatory medicaments, but with meticulous attention to maintenance of blood pressure and a patent airway. One case was treated more strenuously with amphetamine. There was one death in the series, a mortality of 1.06%.

Summario in Interlingua

Durante le periodo quinquenne ab 1953 ad 1958, 140 patientes esseva admittite al Hospital St. Vincent con un diagnose de intoxication per barbiturato. Iste communication concerne le 95 patientes qui esseva inconscie como resultato de intoxication per barbiturato e qui representava un problema therapeutic. Le serie include un morte. Le analyse del datos indica que le plus importante aspectos del tractamento es (1) le mantenentia de patente vias aeree, (2) le mantenentia del tension de sanguine per medio del uso de agentes vasopressori, e (3) le plus meticulose assistentia hospitalari, con attention special prestate al signos vital, al postura del patiente, e al oculos, al pelle, e al bucca del patiente. Solmente un del patientes in iste gruppo recipeva un dose therapeutic de drogas stimulatori. Le altere 94 recipeva nulle tal. Lavage gastric esseva executate in multes del casos. Esseva notate nulle indication que iste mesura esseva benefic. Del altere latere, cinque del patientes subjicite a lavage gastric aspirava contento gastric. In duo de illes le resultante obstruction del vias aeree esseva satis sever pro justificar tracheotomia. In duo alteres, collapso vasomotori sequeva le intubation gastric. In despecto de numerose casos de coma prolongate, tracheotomia elective esseva considerate como necessari in un occasion solmente. Penicillina e altere antibioticos esseva administrate "prophylacticamente" a 61 patientes. Pneumonia se disveloppava in duo de iste patientes e febre in 12 alteres. Le gruppo includeva un caso de pneumonia in que nulle antibiotico esseva usate. Le cifras de mortalitate in iste serie de patientes es multo plus favorabile que le cifras reportate per altere autores pro series de patientes subjicite a vigorose therapias analeptic.

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A LOCAL OUTBREAK OF TRICHINOSIS *

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Introduction

Trichinosis, a helminth infestation harbored by 25% of North Americans at some time during their lives, causes death in 5 to 6% of symptomatic patients.[1] Although public health measures have caused some decline in the number of reported trichinosis cases in the United States, the disease definitely has not been eliminated. In some areas, it is quite common. Between 1949 and 1951, 0.6% of grain fed hogs in the midwest and 11.2% of garbage fed hogs in the east were infested with *Trichinella spiralis* larvae.[2] There is also an immense reservoir of this helminth in rats and other rodents. Hence, there seems little doubt that trichinosis will remain a public health menace for many years.

The Lykens Outbreak

This study reports a local outbreak of trichinosis which occurred in Lykens, Pennsylvania, and the clinical, epidemiologic, and sociologic investigations concerned therewith.

During an eight-day period, six patients with trichinosis were admitted to the Harrisburg Polyclinic Hospital. All were referred by one physician in Lykens, Pennsylvania, a rural community, population 2,500, about 34 miles from Harrisburg, Pennsylvania. Two of the more interesting and unusual cases are described.

Case 1: A 48-year-old white male was admitted October 24, 1958, with diarrhea and weakness. Seventeen days previously there had been a sudden onset of watery diarrhea, followed by vomiting and persistent diarrhea (10 to 20 stools per day). Chills, mild dyspnea, anorexia, headache, and malaise were also present. There was no muscle pain. Physical examination revealed a dehydrated male with a temperature of 100° F. and hyperactive peristalsis. Laboratory studies revealed a white blood cell count of 26,000/cu. mm. with 40% neutrophils, 49% eosinophils, and 11%

* Received for publication October 14, 1960.

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lymphocytes, a sedimentation rate of 16 mm./ hr., and a negative Widal test. Stools were negative for bacterial and parasitic pathogens. Proctoscopic examination and barium enema were noncontributory. A trichinella skin test was positive in 20 minutes, but negative in 24 hours. Gastrocnemius biopsy revealed encysted *Trichinella spiralis* larvae (Figure 1).

Because of failure to control the diarrhea on conservative management, ACTH was administered, producing an immediate cessation of diarrhea. On discharge, November 11, 1958, the white blood cell count was 17,000/cu. mm. with 48% eosinophils. On January 9, 1959, a trichinella complement fixation test was negative, and bentonite flocculation was 1:110. Follow-up examination after six months was negative, and blood count was normal.

Case 6: A 36-year-old white male was admitted on November 1, 1958, with a three-week history of generalized myalgia and pruritis of the left arm and right lower extremity. Left wrist drop and weakness of the grip had developed at the onset on

FIG. 1. Cross section of encysted *Trichinella spiralis* larvae, with surrounding inflammatory reaction (case 1).

October 10. High fever, chills, occipital headache, and transient periorbital swelling were continuously present. Insomnia and fatigue were major complaints on admission. Physical examination revealed a temperature of 102° F., left wrist drop, left biceps weakness, paresis of the fourth and fifth fingers of the left hand, and right anterior tibial weakness with foot drop. The Achilles reflex was absent on the right and the biceps reflex on the left was weak. Muscle tenderness was minimal.

Laboratory examination revealed a white blood cell count of 10,700/cu. mm. with 45% neutrophils, 47% eosinophils, 1% basophils, and 7% lymphocytes. Spinal fluid pressure was 270 mm., with normal chemistries and no cells. Trichinella skin test was positive in 20 minutes, but negative in 24 hours. Trichinosis complement fixation was 1:512, bentonite flocculation 1:5,280. Gastrocnemius biopsy revealed encysted *Trichinella spiralis* larvae.

The patient was treated with ACTH and the temperature became normal in three days. Mild pedal edema developed. Mild foot and wrist drop were still present

when he was discharged on November 17, but there was improvement in muscle function. At this time a white blood cell count showed 10% eosinophils. All muscle weakness disappeared within eight weeks. On January 9, 1959, trichinella complement fixation was negative, but the bentonite flocculation was 1:5,120. Follow-up examination in six months revealed an absent Achilles reflex on the right and slight edema of the right ankle. Malaise and lethargy were minor symptomatic residuals. There were no other neurologic deficits and the blood count was normal.

Case Study Work: Visitations to the homes of these six hospitalized patients, and to the home of another family exhibiting suspicious symptoms, were conducted November 8, 1958, by hospital clinicians. An attempt was made to elicit pertinent symptoms occurring during the preceding six weeks. Each family member was questioned as to the type of meat eaten, individual pork eating habits, the dates and places of pork purchases, a detailed account of methods of cooking pork in the home, as well as the dates of pork ingestion and onset of illness. Differential and white blood cell counts were performed on all patients. During the investigation, the name of another person with suggestive symptoms was obtained and his family was investigated. Inter-

TABLE 1A

Proved Trichinosis Cases

Number	Fam. No.	Init. (Age)	Dt. Pork Purch. (Dt. Range)	Ingest. Pork (Dt. Range)	Dt. 1st Sy.	Place Pork Purch.	Sugg. Sy.	Spec. Rx.	Peak WBC (per cubic millimeter)	Peak Eosin. Ct.	Trich. Skin T.		C.F.	B.F.	Pork Eat. Hab.
											20 Min.	24 Hr.			
1	I	H.S. 48	9–25 10–4	10–5	10–7	ABC	Yes	ACTH	26,000	55	+	−	0	1:10	Raw sausage "taster"
2	II	F.D. 26	9–25 9–30	9–28 10–1	10–1	A	Yes	Terra-mycin	10,300	25	+	+	0	1:320	Tasted raw sausage
3	III	D.N. 28	10–1 10–8	10–14	10–19	A	Yes	Corti-sone	25,000	56	+	+	0	1:640	Raw sausage "taster"
4	IV	D.A. 35	10–1 10–6	10–5 10–10	10–10	A	Yes	ACTH	19,850	63	+	−	0	1:320	Raw sausage "taster"
5	V	RaS. 52	10–12	10–12	10–14	A	Yes	ACTH	19,000	58	+	+	0	1:40	Cooked pork
6	VI	A.H. 36	10–6 10–7	10–7 10–10	10–9 10–10	A	Yes	ACTH	10,700	47	+	−	1:512	1:5,280 1:5,120	Raw sausage "taster"
7	VIII	M.S.	10–5 10–12	10–10 10–14	10–15	AE	Yes	Anal-gesics					1:16	1:10	Raw sausage "taster"

Abbreviations used in Tables 1A, B, and C:
Family Number = Fam. No.
Initials = Init.
Date Range = Dt. Range
Date of Pork Purchase = Dt. Pork Purch.
Ingestion of Pork = Ingest. Pork
Date of First Symptom = Dt. 1st Sy.
Place of Pork Purchase = Place Pork Purch.
A, B, C, D, E refer to local retail stores in or near Lykens, Pennsylvania.
Suggestive Symptoms = Sugg. Sy.
Trichinella Skin Test = Trich. Skin T.
Complement Fixation = C.F.
Bentonite Flocculation = B.F.
Pork Eating Habits = Pork Eat. Hab.

TABLE 1B

Suspected Trichinosis Cases

Number	Fam. No.	Init. (Age)	Dt. Pork Purch. (Dt. Range)	Ingest. Pork (Dt. Range)	Dt. 1st Sy.	Place Pork Purch.	Sugg. Sy.	Spec. Rx.	Peak WBC (per cubic millimeter)	Peak Eosin. Ct.	Trich. Skin T.		C.F.	B.F.	Pork Eat. Hab.
											20 Min.	24 Hr.			
8	I	R.S. 17	9–25 10–4	10–5	10–19	ABCD	Yes		7,400	1			0	0	Ate raw sausage
9	I	T.S. 44	9–25 10–4	10–5		ABC	No		10,000	18			0	0	Tasted raw pork
10	II	G.D. 33	9–25 9–30	9–28 10–1	10–8	A	Yes		6,900	1			0	0	Cooked pork
11	II	B.D. 2½	9–25 9–30	9–28 10–1		A	No			8			0	0	Cooked pork
12	III	E.N. 28	10–1 10–8	10–14	10–14 10–19	A	Yes		11,400	3			0	0	Cooked pork
13	III	B.N. 6	10–1 10–8	10–14		A	No		13,800	7			0	0	Cooked pork
14	IV	J.K. 68	10–1 10–6	10–5 10–10	10–17	A	Yes		15,100	58			0	0	Raw sausage "taster"
15	VI	R.H. 4	10–6 10–7	10–7 10–10		A	No			7			0	0	Cooked pork
16	VII	DAS 3	10–10	10–10 10–19	10–24	A	Yes		12,900	7			0	0	Fed raw sausage
17	VII	B.S. 25	10–10	10–10 10–19	11–3	A	Yes		11,600	2			0	0	Ate raw sausage

viewed also were employees of a market thought to be handling infested pork. Public health officials later conducted a similar, but more extensive, investigation of an epidemiologic nature. Serologic studies were performed at this time.

Of the 40 people studied during the investigation, six were hospitalized patients, 22 were relatives of hospitalized patients, seven were from two other family groups, and five were employees of the market mentioned earlier. All six hospitalized patients, and one patient not hospitalized, were proved to have trichinosis (Table 1A). Ten other persons were suspected of being infested (Table 1B). There was no clinical, hematologic, or serologic evidence of infestation in the employees of the retail market. Of the 10 trichinosis "suspects," six had symptoms suggestive of trichinosis, including three unrelated persons (#8, #10, #12) who had watery diarrhea, myalgias, malaise, and anorexia simultaneously with similar symptoms in hospitalized patients. One 68-year-old female (#14) suffered for five days with severe pains in the arms, slight fever, and fatigue. Two other people, mother and daughter (#17 and #16), had vomiting, diarrhea, and fever, accompanied by myalgias, lassitude, and sore throat. Patient #17, in addition, had severe frontal headache and pain on extraocular

TABLE 1C

Exposed Personnel, Not Infested

Number	Fam. No.	Init. (Age)	Dt. Pork Purch. (Dt. Range)	Ingest. Pork (Dt. Range)	Dt. 1st Sy.	Place Pork Purch.	Sugg. Sy.	Spec. Rx.	Peak WBC (per cubic millimeter)	Peak Eosin. Ct.	Trich. Skin T.		C.F.	B.F.	Pork Eat. Hab.
											20 Min.	24 Hr.			
18	I	L.S. 11	9–25 10–4	10–5	10–24	ABC	No		6,900	1			0	0	Cooked pork
19	II	T.D. 4½	9–25 9–30	9–28 10–1		A	No		7,600	2			0	0	Cooked pork
20	III	J.N. 8	10–1 10–8	Does not eat meat			No		9,900	3			0	0	Does not eat meat
21	III	D.N. 4	10–1 10–8	10–14		A	No		11,300	5			0	0	Cooked pork
22	IV	G.A. 37	10–1 10–6	10–5 10–10		A	No		8,600	1			0	0	Cooked pork
23	IV	C.A. 10	10–1 10–6	10–5 10–10		A	No		8,300	0			0	0	Cooked pork
24	IV	D.A. 5	10–1 10–6	10–5 10–10		A	No		7,100	0			0	0	Cooked pork
25	V	RuS. 47	10–12	10–12		A	No		6,800	0			0	0	Cooked pork
26	VI	K.H. 34	10–6 10–7	10–7 10–10		A	No		8,500	2			0	0	Cooked pork
27	VI	L.H. 1	10–6 10–7	10–7 10–10		A	No			0			0	0	Cooked pork
28	VI	A.H. 9	10–6 10–7	10–7 10–10		A	No		9,300	2			0	0	Cooked pork
29	VI	K.H. 13	10–6 10–7	10–7 10–10		A	No		8,500	1			0	0	Cooked pork
30	VI	D.H. 15	10–6 10–7	10–7 10–10		A	No		8,800	3			0	0	Cooked pork
31	VI	J.H. 17	10–6 10–7	10–7 10–10		A	No		9,600	0			0	0	Cooked pork
32	VII	D.S. 5	10–10	10–10 10–19		A	No		10,100	1			0	0	Cooked pork
33	VII	R.S. 24	10–10	10–10 10–19		A	No						0	0	Cooked pork
34	VIII	C.S.	10–5 10–12	10–10 10–14		AE	No						0	0	Cooked sausage
35	VIII	B.S.	10–5 10–12	10–10 10–14		AE	No						0	0	Cooked sausage
36		E.S.					No		8,900	1			0	0	Owner of A—Samples sausage
37		L.S.					No						0	0	Wife of owner—Samples sausage
38		H.U.					No						0	0	Employee of A—Samples sausage
39		J.U.					No						0	0	
40		E.P.					No						0	0	

movement. None of these six patients had serologic evidence of trichinosis, although one (#14) had a 15,000 white blood cell count with 58% eosinophils. Four other patients were suspected only because of eosinophilia (one having 18%), but none was symptomatic. All had negative trichinella serologic tests (Table 1B).

Clinical Aspects

Diagnosis: In the October, 1958, Lykens outbreak, the diagnosis of trichinosis was established in seven cases. In six of these cases, diagnosis was substantiated by eosinophilia, serologic tests, skin tests, and muscle biopsies. In one case, serologic data were thought to substantiate the clinical impression. All seven proved cases were symptomatic. Case work in Lykens revealed four other people with suggestive symptoms only, two people with both suggestive symptoms and eosinophilia, and four others with eosinophilia. None of these 10 "suspects" had positive trichinella complement fixation or bentonite flocculation tests.

All seven patients with confirmed diagnoses were of middle or low socioeconomic groups and all were adults ranging from 26 to 52 years of age. Four females who prepared sausage admitted tasting raw tidbits. Two of the three afflicted males also admitted eating uncooked sausage.

The incubation period was established within a narrow range for each individual. Absence of early gastrointestinal symptoms in some patients made calculation difficult. The latent period in all seven proved cases varied from two to seven days.

Many authors have pointed out the potential difficulties in making the diagnosis of trichinosis. Hall[3] lists about 50 diseases which have been diagnosed in patients subsequently proved to have trichinosis. Glomerulonephritis, cirrhosis, rheumatic myocarditis, focal central nervous system lesions, encephalitis, sinusitis, and influenza may be readily confused. The symptoms observed in the confirmed cases of the Lykens outbreak were protean. Headache, malaise, fever, chills, weakness, myalgia, and periorbital edema were most frequently observed. Muscle tenderness was common. Gastrointestinal symptoms were present in two-thirds of the cases. The variety and alteration in the signs and symptoms of the hospitalized patients are seen in Table 2. The diverse manifestations and evolution of symptoms of trichinosis are explained by the ever-changing position of the *Trichinella* larvae before definitive "larvae position" occurs.

Enteritis: The prolonged diarrhea of 27 days' duration noted in case 1 responded promptly to corticotropin and has not recurred to date. The reasons for the chronicity of the diarrhea and sudden remission remain a matter of conjecture. Gould[1] states that in a small number of persons with gastrointestinal symptoms, the diarrhea may be a serious event, particularly if it is severe, long maintained, or if it occurs in a debilitated individual. Ingestion of a large number of living larvae may produce a fatal enteritis.

Myocardial and Nervous System Involvement: In the hospitalized patients, there was no definite evidence of myocardial involvement, so often a fatal complication of trichinosis. However, three patients did have nonspecific T wave changes electrocardiographically; all tracings later returned to normal. Likewise, in this series, there was no direct evidence of central nervous system involvement, despite the fact that, in three patients who had spinal punctures, all had elevated spinal fluid pressures. There have been many reported cases[4, 5] in which central nervous system involvement has caused death or has left permanent neurologic residuals. Ober[6] has sug-

TABLE 2

Changing Signs and Symptoms in Hospitalized Patients

Sign or Sy.	1st Sy.	Subseq. Sy.*	C.C. on Adm.	C.C. on Disch.	R. in 6 Mo.
Headache	2	5, 6	1, 2, 3, 4, 6		
Malaise		1, 2, 3, 4	1, 2, 3, 6		6
Fever		1, 2, 3, 4, 5, 6	1, 2, 3, 4, 5, 6		
Periorbital edema	3	2, 4, 5, 6	2		2
Weakness				3, 6	
Myalgia	5	2, 6	2, 3, 4, 5	3	
Chills		1, 2, 4, 6	2		
Facial swelling		3		2	
Muscle tenderness		3, 5, 6	2, 3, 4, 5, 6		
Vomiting	1, 4	3			
Leg swelling				4	3, 6
Diarrhea		1, 5	1, 4, 5		
Abdominal cramps	1		5		
Stiff neck			2		
Cough	5	4, 5			
Pruritis		6		4	
E.O.M. pain		4, 5			
Insomnia			1, 6	2	
Constipation	4				
Wrist drop	6	6	6	6	
Foot drop			6	6	
Dysphagia		3			
Localized areflexia					6
Fatigue		1	6	4, 5	4
Dysuria		1			
No symptoms				1	1, 5

* Average time between onset of sy. and hospital admission = 18 days (range 9–26 days).

Number refers to patient (Table 1A). Sy. = Symptom; R. = Residual Symptom; C.C. = Chief Complaint; E.O.M. = Extraocular Movement.

gested that the lack of larval encystment in heart and brain may actually permit greater damage to these structures. Peripheral neuropathy resulting from trichinosis is not a common finding. In the large Liverpool, England, epidemic in 1953, wrist drop was seen in only 1.2% of the cases.[7] Case 6 in the present study had wrist drop among his earliest symptoms, and subsequently developed foot drop. Neurologic deficits persisted for about eight weeks and the right Achilles reflex was permanently lost. Roehm[8] states that peripheral nerve paralysis, presumably a toxemic effect, may be the presenting complaint in trichinosis.

Residual Signs and Symptoms: The residuals found in the seven proved cases (six months after the acute illness) should be explained. While the persistent edema of one leg found in three * patients is probably caused by lymphatic obstruction from previous inflammation, it is difficult to explain the persistent periorbital edema found in a fourth patient. That the *Trichinella* larvae are antigenic is shown by the high eosinophil counts and the presence of antibodies in skin and blood which yield positive skin and serologic tests. Hence, it is believed that a localized hypersensitivity to trichinella protein could account for this finding.

Laboratory Abnormalities: Eosinophilia ranged from 25% to 63%, and leukocytosis from 10,000 to 26,000/cu. mm. in the hospitalized patients. Eosinophilia is reported to appear within one or two weeks and is said to persist from eight to 12 months.[9] In this series, all had normal white and differential counts after six months. In the 10 suspected, but not verified, cases, six had eosinophilia ranging from 7% to 58%.

All seven proved cases exhibited positive bentonite flocculation tests in varying dilutions, but only two patients had positive complement fixation tests. Complement fixation antibodies cannot be detected for three weeks following ingestion of infested meat. The bentonite flocculation test is reported to have a greater sensitivity than the complement fixation test and supposedly demonstrates the presence of antibodies earlier.[10] Moreover, it is more easily performed. The complement fixation test supposedly remains positive longer than the bentonite flocculation test, but the present study did not support this opinion. The sensitivity of the complement fixation test, as performed on a routine basis, is very low, and is not advised as a diagnostic study. It has been stated that the level of the bentonite flocculation or complement fixation titer is not generally correlated with the severity of the clinical manifestations.[10] The serologic reaction appears to be an individual response, and those who are acutely and seriously ill do not necessarily develop a high titer in either test.

Skin tests for *Trichinella* were performed on all six hospitalized patients. Three cases were positive in both the 20-minute and the 24-hour reading; three cases were positive only in the 20-minute reading. The skin test does not become positive until the second week of the disease. It is usually quite specific. The immediate reaction becomes weaker after a few years and usually disappears within seven.[9]

Sedimentation rates in the hospitalized patients averaged 5 mm./hr. over the expected top normal sedimentation rate, substantiating Roehm's report in 1954 that the "relatively low sedimentation rate was an integral part of the hematologic response in trichinosis." [8]

Epidemiology of the Lykens Outbreak

Interviews of the patients and their families revealed that, although the families had purchased pork products from many sources, there was one

* Includes the unhospitalized proved case, #7.

source common to all purchasers (Table 1A). Pork purchased from sources B, C, D, and E consisted of hams and roasts, cuts which require cooking before eating. Fresh sausage had been purchased by all families from source A between September 25 and October 12. This general food market (source A) was operated by the owner, who was not registered with or licensed by the Pennsylvania Department of Agriculture to manufacture meat products (as required of all meat processors by law). The operator manufactured the sausage from raw pork trimmings of many carcasses accumulated over several weeks. During the 18-day period in question, source A received over 30 orders of pork from four wholesale meat packers. Each order consisted of many cuts originating from many carcasses. Investigation of the wholesalers revealed that two of the packers maintained full time veterinary meat inspectors, while two other packers had no inspection. The latter, however, were approved and licensed by the Pennsylvania Department of Agriculture. Most of the packers purchased meat from local sources; only two packers bought hogs from out of state. All wholesalers emphasized that no known garbage fed hogs were ever purchased. In view of the multiple sources of pork supplies and the difficulty in identifying individual carcasses, it was impossible to trace the hogs back to the farms of origin for additional data on feeding practices.

It should be noted that, regardless of the level of meat inspection, whether performed by federal, state, or local governmental authorities, no examination is ever made for *Trichinella spiralis*. A government stamp on meat stating "Inspected and Passed" does not insure freedom from helminth infestation. Although all states now have laws requiring thorough cooking of garbage at not less than 125° F. for at least 30 minutes before it is fed to hogs, this regulation will not eliminate other reservoirs of infestation that may be present in rats and other small mammals in feeding lots.

Only one patient in the seven cases denied eating raw sausage. Infestation of this individual might be explained by his use of a kitchen utensil which had been in direct contact with the sausage in the course of preparation.

Since only seven people suffered serious illness in the Lykens incident, it is of considerable interest that other family members who ate the same meat were not seriously affected (Table 1C). Since sausage often is made from the trimmings of numerous hog carcasses, the meat from one infested hog is well diluted with other meat. It is believed that far more persons in the Lykens area are now hosts to *Trichinella* larvae than were initially suspected. This dilution factor hypothesis is supported by Gould, who states that, with dilution, the chance of becoming infected in some degree from such a product when eaten raw is increased, whereas the likelihood of becoming heavily infected with a sufficiently large number of *Trichinellae* to produce clinical trichinosis is greatly decreased.[11]

Table 3 indicates that Pennsylvania trichinosis statistics do not parallel

the downward trend observed in national statistics during the past 10 years. It is believed that better epidemiologic investigations, reporting, and improved case finding technics may be factors, but it is to be noted that Germans, Italians, and rural inhabitants are those most frequently involved in trichinosis outbreaks in Pennsylvania. It is known that these three population groups have a penchant for raw pork and raw pork products. So long as these group dietary preferences persist, there seems little likelihood that trichinosis can be eliminated as a public health menace.

TABLE 3

Reported Trichinosis Cases

Year	Pennsylvania	United States
1949	22	353
1950	14	327
1951	17	393
1952	14	367
1953	18	395
1954	16	277
1955	17	264
1956	59	262
1957	11	178
1958	26	176
1959	23	227
1960	8 (to date)	Not yet available

SUMMARY AND CONCLUSIONS

A trichinosis outbreak in a rural Pennsylvania town is noted. Prolonged diarrhea and peripheral nerve involvement were among the more unusual manifestations observed. Residual leg edema and persistent periorbital swelling were present in some patients six months after the acute illness. Laboratory methods of diagnosis are briefly discussed. Epidemiologic investigations showed the common source of the outbreak to be fresh sausage, manufactured locally from numerous carcasses, originating in four licensed wholesale meat packing establishments. Seven patients, all seriously ill, were proved to have trichinosis. Case work led to a suspicion of trichinosis in 10 other persons, most of whom were relatives of those hospitalized. It is believed, however, that, because of the dilution factor in the sausage preparation, many other people in the community had subclinical infestations.

SUMMARIO IN INTERLINGUA

Trichinosis, ben que su incidentia declina, es non ancora eliminate in le Statos Unite, e illo continua esser un menacia pro le sanitate public proque porcos—in certe casos—es alimentate con rejectos de menage e proque il existe reservoirs natural in rodentes. Trichinosis in Pennsylvania es le plus commun in personas de ancestria german o italian, i.e. in le gruppos del population que sole mangiar crude productos porcin.

Es describite un eruption de trichinosis in un communitate rural. Le symptomas commun esseva mal de capite, malaise, febre, algor, debilitate, myalgia, e edema

periorbital. Gravamines gastrointestinal esseva commun. Prolongate episodios de diarrhea e affectiones de nervo peripheric esseva inter le manifestationes plus tosto inusual. Residuos de edema de gamba e periorbital esseva presente in certe casos usque a sex menses plus tarde.

Es discutite methodos laboratorial de diagnose. Le maximos de eosinophilia variava inter 25 e 63 pro cento, sed iste numeration esseva normal in omne le patientes al fin de sex menses. Le test de flocculation a bentonite esseva plus utile in le diagnose que le test a fixation de complemento, sed nulle titro positive esseva trovate in ulle del non provate e solmente suspicite casos.

Le investigation epidemiologic monstrava que le fonte del eruption esseva salsicia fresc, fabricate localmente ab numerose corpores de porco originari de quatro establimentos abattitori con licentias statal. In septe patientes, le presentia de trichinosis esseva provate, e sex de istes admitteva que illes habeva mangiate salsicia crude. Le investigation del casos resultava in un suspicion de trichinosis in 10 altere subjectos, principalmente membros de familia del hospitalisatos. Viste le factor de dilution in le preparation de salsicias, il debeva esser supponite que multe altere individuos in le communitate habeva infestationes subclinic.

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CASE REPORTS

PURPURIC CHICKENPOX: REPORT OF A CASE, REVIEW OF THE LITERATURE, AND CLASSIFICATION BY CLINICAL FEATURES *

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Purpura is an unusual complication of chickenpox. On the basis of differences in etiology, clinical manifestations, prognosis, and therapy, five major purpuric syndromes may be recognized in this disease: febrile purpura, malignant chickenpox with purpura, postinfectious purpura, purpura fulminans, and anaphylactoid (Schönlein-Henoch) purpura. In addition, bleeding may result from secondary infection, with or without gangrene, or, more rarely, from hemorrhagic nephritis.

The purpose of this communication is to report a case of febrile purpura, to review the literature pertinent to bleeding associated with chickenpox, and to delineate the differential features of the major syndromes.

Case Report

A 26-year-old unmarried white male was admitted to Walter Reed Army Hospital, Fort Detrick, Maryland, on January 29, 1958, with complaints of malaise, fatigue, headache, anorexia, feverishness, chilly sensations, night sweats, and joint aches of 48 hours' duration. On the morning of admission a mild, nonproductive cough developed. Physical examination the previous day had been within normal limits except for oral temperature of 100.4° F.

The patient was unaware of ever having had chickenpox, and knew of no unusual bleeding tendency. Two years previously his mother had developed "low platelets" during a febrile illness. Twenty-five days prior to onset of symptoms he had visited a niece who was in the pre-eruptive stage of chickenpox.

Physical examination revealed a young man in no distress. Rectal temperature was 102.2° F.; pulse, 80; respiration, 20; blood pressure, 130/70 mm. Hg. There was a pruritic macular rash of the forehead. Scattered vesicles on an erythematous base, characteristic of chickenpox, were observed on the neck, scalp, trunk, and buccal mucosa. No petechiae were noted. There was generalized, mild adenopathy. The palpebral conjuctivae were suffused. The spleen was not palpable. Healed abrasions of recent origin proximal to the left patella were noted. The remainder of the physical examination was unremarkable.

Admission hemogram was as follows: white blood cells, 2,600/cu. mm. with 34% segmented neutrophils, 28% band forms, 31% lymphocytes, 5% monocytes, 1% eosinophils, and 1% plasma cells; hemoglobin, 14.4 gm./100 ml.; hematocrit, 44%; corrected sedimentation rate (Wintrobe), 15 mm./hr. There were slight anisocytosis

* Received for publication December 14, 1959.
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and diminution in platelets on stained smear. Urinalysis revealed a rare red blood cell per high power field. C-reactive protein was 4-plus. A standard, six-foot roentgenogram of the chest revealed clear lung fields and normal cardiac silhouette.

On the second hospital day several dozen petechiae were noted on the anterolateral aspect of the legs. Platelets numbered 55,000/cu. mm. (Fonio method *). Inflation of a sphygmomanometer cuff to 100 mm. Hg for five minutes (Rumpel-Leede test) produced numerous petechiae on the forearm.

Bleeding into vesicles or areolae was not noted at any time. Crops of new vesicles appeared for the next three days, at which time the temperature returned to normal and the lesions crusted. Petechiae disappeared during defervescence, and by the sixth hospital day the platelet count had returned to normal (Figure 1). The

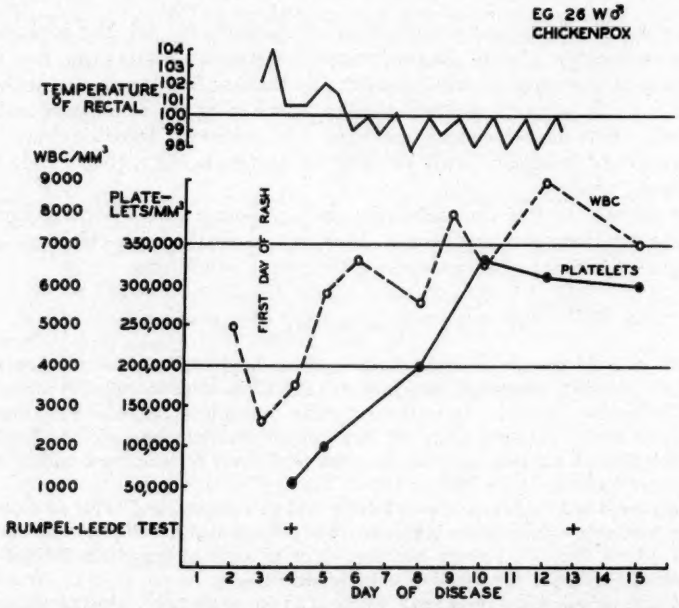

FIG. 1. Febrile purpura. Note inverse relationship of platelet count and temperature. Zone of normal platelet counts (200,000 to 350,000/cu. mm.) is demarcated.

abrasions proximal to the knee had taken on a violaceous hue. On the eleventh hospital day the Rumpel-Leede test was positive, bleeding time was 1 minute, 46 seconds, and coagulation time in glass was 9 minutes, 53 seconds. The patient made an uneventful recovery and was returned to full duty.

Thirteen weeks later the Rumpel-Leede test was again positive, but less so than previously. Platelets numbered 218,000/cu. mm., and physical examination was within normal limits.

Comment: During the early, febrile stage of chickenpox in a young soldier, petechiae appeared on the lower extremities, and cutaneous bleeding occurred in a recent abrasion. With defervescence no new hemorrhagic manifestations

* Normal for this laboratory, 200,000 to 350,000/cu. mm.

developed, and circulating platelets returned to normal levels. The Rumpel-Leede test was positive during the eruptive phase and in the thirteenth week of convalescence. This case is a typical example of febrile purpura.

Review of Literature

To study purpura in chickenpox, the pertinent literature was reviewed, except for the history of purpura fulminans prior to 1914. (A recent report has comprehensively discussed this syndrome.[1]) Sixty-eight cases of cutaneous bleeding complicating this exanthem were found. On the basis of differences in etiology, clinical manifestations, prognosis, and therapy, purpuric chickenpox was then classified into five syndromes.

The number of published cases of each type should not be construed as an indication of their true prevalence, since the most common form, febrile purpura, is benign and rarely reported. Eight of the 68 cases could not be classified because of insufficient data.

Febrile Purpura: According to Stroh, "A hemorrhagic eruption in varicella . . . occurs in about two per cent of cases."[2] Comby states, "Sometimes the bullae of varicella become hemorrhagic,"[3] and another author notes, "A violet tint in the papules, a few intravesicular hemorrhages, and scattered petechiae may frequently be observed in varicella."[4] Such benign bleeding, occurring in conjunction with temperature elevation, may be termed "febrile purpura." Only seven such case reports were found,[5-10b] and it was not listed as a complication of chickenpox in two series totaling 3,309 patients.[11a, 12]

Febrile purpura may occur in an adult or in a child of either sex. Although bleeding usually is noted on the first or second day of a mild varicelliform eruption, as in the subject of this case report, it has appeared up to five days before or two days after onset of rash. The vesicles and surrounding areolae are the most common sites of hemorrhage, but petechiae about the ankles are frequently seen. Ecchymoses, epistaxis, and melena may develop. Bleeding persists for the duration of fever, and perhaps for a short time thereafter.

Platelets are usually depressed, and may number less than 50,000/cu. mm. Bleeding time may be prolonged, and there are defective clot retraction and increased capillary fragility. Clotting time is normal.

The course and prognosis are those of the uncomplicated disease. Treatment is directed toward replacement of blood loss, if extensive. Steroid therapy is not ordinarily warranted, in view of the transient and benign nature of the bleeding.

It is likely that the thrombocytopenia which normally accompanies chickenpox[13] and certain other infectious diseases[14a-16] is due, at least in part, to fever,[14a, b] as illustrated in the figure. This can be demonstrated experimentally in the rabbit. In this animal, fever induced by radiant heat is accompanied by substantial depression of circulating platelets as a result of megakaryocyte damage.[17] Similarly, in heat stroke in humans, thrombocytopenia as low as 22,300 and injury to megakaryocytes with reduction in their numbers were noted as early as six hours after onset of hyperthermia, and appeared to be directly related to the height of the fever.[14b]

Increased rate of platelet removal by "platelet loading" may also play a role in the thrombocytopenia of infection.[14a]

Bleeding does not occur in the absence of damaged blood vessels, no matter how low the platelet count.[18-23] Thus, Bedson[24] was unable to produce purpura in the rabbit by intravenous injection of agar, which resulted in considerable diminution in platelets but no damage to blood vessels, although purpura followed injection of an antiplatelet serum which caused both capillary damage and thrombocytopenia.[24, 25] Thrombocytopenia frequently accompanies states of increased capillary fragility, and may potentiate existing bleeding.[21, 23]

Parasitization of endothelial cells of the smaller blood vessels of the skin and other organs is a constant feature of uncomplicated varicella.[26-29] These cells swell and occasionally occlude the vessel[26, 27, 30] or undergo necrosis.[29] Thrombosis[27] and perivascular cellular infiltration may occur.[29, 30] Although this damage may conceivably result in hemorrhage, it probably plays little part in febrile purpura, inasmuch as severe vascular involvement is uncommon in malignant chickenpox with purpura, and bleeding in uncomplicated chickenpox is infrequent, rather than the rule.

Capillary dilatation, congestion, and hemorrhage without visible damage to vessels are outstanding histologic manifestations of artificially induced fever[17, 31-33] and of heat stroke.[14b] Similar changes occur in uncomplicated chickenpox.[1, 26, 29, 34-37] In heat stroke the number and severity of visceral hemorrhages are directly proportional to the duration of hyperthermia, and constitute one of the most striking features at autopsy.[14b]

Elevated body temperature produces cutaneous hyperemia, increased blood flow, and increased capillary pressure,[38] which may lead to rupture of vessels[33] and edema.[38, 39] The amount of negative pressure to the skin, as applied by suction cup, which is required to produce petechiae, is therefore much reduced in febrile states (increased capillary fragility).[15, 22, 33, 40a, b] Pronounced changes in capillary function may result from variations in temperature supposedly within physiologic limits.[41]

There is wide individual variation in the pressure required to rupture capillaries.[22, 42, 43] Between 0.5 and 1.4% of healthy young adults have markedly diminished capillary resistance refractory to vitamin C or to flavonoid therapy.[42, 43] It is tempting to speculate whether these persons are the same 2% who are said to develop febrile purpura in chickenpox.[2] The capillary resistance of the subject of this case report, following recovery from chickenpox, was abnormally low, as judged by the Rumpel-Leede test, but quantitative studies with suction applied to the skin were not performed.

Metabolic changes attendant upon febrile states may be responsible in part for extravasation of blood. Hypocalcemia and changes in hydrogen-ion concentration adversely affect the production of intercellular cement substance of capillaries, and erythrocytes are extruded through such damaged vessels.[44] Fever has been postulated to have similar action,[19] but direct evidence is lacking.

In summary, it would appear that the pathogenesis of febrile purpura in chickenpox is related to increased capillary pressure secondary to cutaneous hyperemia. Metabolic derangements and endothelial damage may play a role in its production, and thrombocytopenia may potentiate it. It is possible, though not proved, that patients who develop febrile purpura have constitutionally lower capillary resistance to pressure changes than does the average person.

Malignant Chickenpox with Purpura: This syndrome is associated with

overwhelming infection, and superficially appears to be analogous to purpura variolosa in smallpox.[45]

Twenty-eight case reports were found in the literature.[2, 4, 28-30, 34-36, 46-62] * Malignant chickenpox with purpura occurs in all age groups and equally in both sexes. It almost always begins within five days of onset of the vesicular eruption, but may not develop until the tenth day. It never appears before the chickenpox rash. Patients are usually toxic, with high fever and delirium, and may develop muscular twitchings, convulsions or coma. Bleeding is sometimes ushered in with fever after a period of normal temperature. It is usually manifested by hemorrhagic vesicles and areolae, and petechiae, purpura, and ecchymoses are not uncommon. Bleeding from the gastrointestinal tract, genitourinary tract, and mucous membranes is frequent. This is the only type of purpura in chickenpox in which hemoptysis occurs. Pneumonia is common, and facial edema is sometimes noted.

Of seven patients in whom platelet counts were performed, five had some degree of thrombocytopenia. The white blood count was variable, ranging from 1,500 to 21,000/cu. mm. Tests for platelet agglutinins and blocking antibodies were negative in one patient.

The severity of this syndrome is reflected in the mortality rate. In this group of 28 patients, 20 succumbed (71%), usually within 48 hours of onset of bleeding. The high mortality rate of malignant chickenpox with purpura parallels that of a similar syndrome in other infectious diseases.[63] In reporting a case with favorable outcome, Ghosh remarked that all previous examples seen at his clinic had been fatal.[62]

Four patients, all of whom died of malignant chickenpox with purpura, received ACTH or steroids for rheumatic fever during the incubation period of chickenpox,[29, 36, 60] and at least 10 other children have succumbed to chickenpox while on these drugs.[64] In one child taking cortisone for urticaria, relapse of chickenpox was recorded,[65] and in another case, hemorrhagic vesicles continued to appear for three weeks after cessation of steroids.[64] An increased tendency toward hemorrhagic rash has been noted in children taking cortisone,[64, 66] although there is evidence that ACTH and steroids markedly increase capillary resistance.[22, 40a, b] In still other cases, no effect of steroids on the rash has been observed.[64]

When chickenpox vesicles appear in persons receiving steroids, Nichols suggests reduction of dosage to "physiologic stress levels," and administration of convalescent serum.[67] Others would discontinue hormones.[10b, 36, 64] Haggerty and Eley would also terminate steroids as rapidly as possible in any susceptible child known to have been exposed to the disease.[64]

Therapy for malignant chickenpox with purpura included blood replacement, convalescent serum, vitamins C and K, and calcium gluconate. None had apparent beneficial effect.

Post-mortem examination was performed in 13 patients. Vascular changes were those described in preceding paragraphs. Extensive hemorrhages occurred in the viscera, serosal surfaces, and brain.[28-30, 35, 36, 46, 51, 56, 57] In one instance, fibrinoid necrosis of cerebral vessels was noted.[35] In a patient with marked thrombocytopenia, bone marrow biopsy revealed diminished platelet formation.[61]

* Olesen,[58] case 2.

Viremia and absence of complement-fixing antibodies were demonstrated in two patients who died on the fourth and seventeenth days of rash, respectively.[29]

Malignant chickenpox with purpura probably results from overwhelming infection with the virus. Although earlier observers were inclined to attribute bleeding to an exceptionally virulent strain of virus, there is reason to believe that individual idiosyncrasy plays the major role.[21] In several instances, siblings or children of the affected individual had mild, uncomplicated chickenpox concurrently.[10b, 52, 56, 59]

Postinfectious Purpura: There were 17 cases of this syndrome in adults and children.[68-80b] * Ten patients were female and six male; the sex was not stated in one. Clinical events were similar to those described by Hirsch and Dameshek for "acute, self-limited thrombocytopenia" complicating other infections and drug therapy.[77]

Bleeding usually begins one to two weeks after appearance of mild chickenpox, but may occur earlier[81] or later, often with fever. The characteristic feature is long duration of bleeding (mean, five weeks), and even longer duration of thrombocytopenia. In most cases the patient returns to good health and the platelet count to normal within four months. Bleeding may sometimes be transient. Hemorrhage occurs in crusted vesicles and areolae, as petechiae, purpura and ecchymoses, and into the intestinal and genitourinary tracts and mucous membranes. The spleen usually is not palpable.

Platelets varied between 16,000 and 42,000/cu. mm. except in two cases where the platelet count was normal. Leukocytes were usually normal or low in number, but occasionally were slightly elevated. In thrombocytopenic cases the bleeding was prolonged, clot retraction impaired, prothrombin consumption decreased, and capillary fragility increased. Anemia was frequent, and necessitated transfusions in some cases.

Bone marrow biopsy was performed in five patients with thrombocytopenia. One biopsy was normal,[80a] one showed megakaryocytic hyperplasia with platelet formation,[78] and two revealed marked diminution to absence of platelet formation with adequate megakaryocytes.[75, 80a] In a fifth case with anemia, there was erythroid hyperplasia, and the megakaryocytes appeared to be normal. In all 18 patients reported by Hirsch and Dameshek, including three with postinfectious purpura secondary to chickenpox, "thrombocyte production was conspicuous by its almost complete absence."[77]

Splenectomy was performed in one patient and appeared to alter favorably the course of the illness.[78] However, Clement and Diamond noted no benefit from this procedure in 20 patients, as compared with controls who had not had surgery.[81] Hirsch and Dameshek reported similar results in a smaller group.[77]

ACTH was administered to one patient in this series[80a] in high dosage for six days. Platelets returned to normal, but bruising, metrorrhagia, and thrombocytopenia later returned. In four months the patient was in good health. Another patient received cortisone for nine days, with favorable response both clinically and in platelet count, but follow-up studies were not reported.[80b] However, Hirsch and Dameshek could detect no alteration in the natural course

* Tancredi,[69] case 1.

of the disease in three patients given ACTH, and suggest platelet transfusions for severe bleeding.[77]

There was one death in this series, and a second patient developed purpura fulminans.

Hirsch and Dameshek state that postinfectious purpura is probably "commoner than generally assumed." [77] It has been reported to follow scarlatina, measles, rubella, infectious mononucleosis, cat-scratch disease,[80a] diphtheria, vaccinia, infectious hepatitis, tuberculosis, malaria, brucellosis, and upper respiratory infections.[21] The nonthrombocytopenic variety is generally the more frequent.[21, 81] The etiology of postinfectious purpura is thought to be on an allergic basis.[21, 77, 80a, 81] Ackroyd suggests an analogy with acute glomerulonephritis following streptococcal disease,[21] and Clement and Diamond have emphasized the need for better bacteriologic studies of the preceding infection.[81] However, although secondary skin infection with streptococci and other organisms is common in chickenpox,[11a] postinfectious purpura is rare. Individuals with this syndrome do not usually give a history of bruising readily in themselves or in their families,[77] but appear to have an increased susceptibility to allergic diseases in general.[81]

Purpura Fulminans: Approximately 100 cases of this syndrome following various infections are known.[1] Of the eight cases complicating chickenpox in this series, all were in patients between two and 11 years of age.[1, 58,* 73, 82-85a,† 85b]

In the typical case, toward the end of the first week of mild chickenpox a subcutaneous ecchymosis appears, most often on the leg or trunk. Within hours the hemorrhage enlarges to form a blue-black, painful, tender mass, sometimes encircling the leg, frequently surmounted by tense bullae containing serous or serosanguineous fluid. Similar ecchymoses soon appear on the same or opposite extremity. The child rapidly becomes toxic and the involved area gangrenous, and hemorrhagic shock supervenes. Petechiae and bleeding into vesicles and areolae may occur. Hemorrhage into the lumen of the intestinal or genitourinary tract or from mucous membranes is usually absent.[85b, 86]

White blood counts of from 16,000 to 58,000/cu. mm. were found in seven patients in whom they were performed. Bleeding and clotting times were usually normal, but low prothrombin times were noted in two of three patients. Three out of five patients had platelet counts of less than 54,000/cu. mm. Capillary fragility was increased in two patients.

Of the eight children with purpura fulminans, three died (two, three, and eight days after onset of bleeding), two required amputation, and one developed postinfectious purpura.[73]

Pathologic study of amputated parts revealed hemorrhagic gangrene [84, 85a] with arterial thrombosis.[84] Post-mortem examination in one case was reminiscent of malignant chickenpox with purpura, with congestion and hemorrhage into internal organs and massive hematoma in the popliteal space.[1]

Bone marrow examination in one patient revealed normal cellular components.

Of four patients receiving ACTH or cortisone therapy, one died[1] and three subsequently underwent amputation, spontaneous or surgical.[84, 85b] Blood

* Olesen,[58] case 1.
† Storrie,[82] case 2.

transfusions, moccasin venom, antibiotics, hot or cold packs, anticoagulants, and antihistaminics appeared to have no effect. Paravertebral block seemed to be of value in returning obliterated femoral pulses.[85] Therapy in eight recovered cases of purpura fulminans reviewed by McGovern included exchange transfusions, methionine, fibrinogen, and massive transfusions.[1] McGovern suggests the use of vitamin K and steroid hormones.

The cause of purpura fulminans is unknown. Quick suggests a relationship to anaphylactoid (Schönlein-Henoch) purpura.[86] Various clotting factor deficiencies, such as Factor V and fibrinogen, have been described.[86] Post-mortem examination in McGovern's case gave no evidence of vasculitis.

Anaphylactoid (Schönlein-Henoch) Purpura: Only one unequivocal case of this syndrone complicating chickenpox was found (Tancredi,[69] case 2).

The salient features of anaphylactoid purpura are well known and are enumerated in Table 1.

Other Forms of Bleeding: Hemorrhagic nephritis secondary to streptococcal infection of the vesicles of varicella or other sites may rarely occur as a complication.[2] The absence of purpura and bleeding from organs other than the kidneys, together with azotemia, edema, and hypertension, should distinguish it from postinfectious purpura.

Cases with vesicle gangrene, sometimes hemorrhagic, have been reviewed recently by Illingworth and Zachary.[87] * The child is frequently malnourished, often has tuberculosis, and secondary infection of the lesions with streptococci, staphylococci, and *Corynebacterium diphtheriae* is common. Toxins produced by these bacteria may be etiologic factors in the development of gangrene, although other explanations have been suggested.

Chickenpox may, of course, occur in individuals with abnormal bleeding tendencies, such as idiopathic thrombocytopenic purpura, hemophilia, or leukemia.

Discussion

The patient reported herein represents a case of febrile purpura, since bleeding was almost inconspicuous and paralleled the fever. The course was otherwise uneventful. Thrombocytopenia was more extreme than is usually seen in acute infection,[14a] and appeared to vary directly with the patient's temperature. The low platelet level may have contributed to the purpuric manifestations, but, for reasons discussed previously, was not the sole factor in its genesis.

The distribution of the petechiae on the legs supports the hypothesis that increased capillary pressure was instrumental in initiating cutaneous bleeding, and the persistently positive Rumpel-Leede test after convalescence may indicate constitutionally low capillary resistance in this otherwise healthy subject. Exact measurements of capillary resistance were not undertaken, but it may be that any febrile illness of sufficient severity would again be accompanied by petechiae in this individual.

Raybaud and Fantin recently reviewed 52 cases of hemorrhagic chickenpox in the literature, including one of their own,[10b] and divided the cases into two types, the *forme ecchymotique simple,* and the *forme purpurique.*† The

* Some of the cases tabulated by Illingworth and Zachary should be characterized as purpura fulminans.

† The review by Raybaud and Fantin was called to this author's attention after preparation of the manuscript.

TABLE 1

Differential Diagnosis of Purpuric Chickenpox

Syndrome	Age	Characteristic Features	WBC Count	Thrombopenia and Abnormal Hemostatic Functions*	Capillary Fragility	Therapy	Fatality Rate
Febrile purpura	Any	Bleeding parallels fever; benign course†	Low or normal	Frequent	Increased	Replace blood lost	None
Malignant chickenpox with purpura	Any	Overwhelming infection;† patient toxic; CNS signs, pneumonia and hemoptysis frequent; precipitated by steroids	Variable	Frequent	Increased	Replace blood lost; convalescent serum; ?ACTH or steroids	High
Postinfectious purpura	Any	Onset often after vesicles crusted; little constitutional reaction; bleeding and thrombocytopenia usually persist for weeks†	Low or normal	Frequent	Increased	Platelet transfusions; splenectomy in selected cases; ?ACTH or steroids	Low
Purpura fulminans	Children	Rapidly progressive hemorrhagic gangrene of trunk or extremities; patient toxic; hemorrhagic shock	High	Frequent‡	Increased	Massive transfusions; exchange transfusions; vitamin K; paravertebral block; ACTH or steroids	High
Anaphylactoid (Schönlein-Henoch) purpura	Children or young adults	Urticaria, melena; joint or abdominal pains; nephritis, edema; crops of purpura; moderate fever	Normal or slightly high	Absent	Usually normal	ACTH or steroids; remove exciting allergen	Low
Hemorrhagic gangrene	Children	Lesions gangrenous; malnutrition and tuberculosis common; pyogenic infection of lesions; toxemia may occur	§	§	§	Supportive care; treat pyogenic infection	High

* Prolonged bleeding time, defective clot retraction, increased prothrombin time.
† Bleeding occurs into skin, vesicles, and areolae, and from nasal and buccal mucous membranes and the gastrointestinal and genitourinary tracts.
‡ Other hemostatic defects also frequent.
§ Insufficient data.

former corresponds to the febrile purpura of this communication, although the authors do not discuss the relationship of purpura to elevation of body temperature. They stress, as we do, the benign nature of this syndrome. Their second category includes both of our divisions: malignant chickenpox with purpura, and postinfectious purpura.

From their review of the literature, Raybaud and Fantin reject the thesis that their *forme purpurique* is attributable to an unusually virulent strain of the varicella virus, a view with which we concur. The nature of the heightened host susceptibility in this syndrome could not be elucidated in every case, although cortisone administration and an underlying hemopathy such as leukemia were incriminated in some instances.

These authors emphasize the prognostic implications of the time of onset of bleeding in relation to the appearance of the characteristic rash, and, in certain syndromes, this is true. In malignant chickenpox with purpura, bleeding usually begins within five days after onset of the rash, and in postinfectious purpura it is usually delayed until the second week of disease. However, bleeding of febrile purpura also occurs early in the course of chickenpox. Since Raybaud and Fantin do not stress the common occurrence of this benign syndrome, clinicians relying on the early appearance of bleeding alone as a poor prognostic sign are likely to be misled, since ecchymoses, epistaxis, and melena have been reported in febrile purpura.[5, 9-10b] Accurate statistics concerning the relative incidence of febrile purpura and malignant chickenpox with purpura would help in clarifying this point.

It is our opinion that time of appearance of bleeding is not the sole factor of prognostic importance in hemorrhagic chickenpox, but is only one of several clinical features, the sum total of which enables the clinician to form an accurate opinion of his patient's status. These other considerations are: age; relation of bleeding to fever; presence of systemic toxicity; presence of central nervous system signs, pneumonia, or hemoptysis; presence of hemorrhagic shock; presence of urticaria, joint pains, nephritis, or edema; presence of gangrene, malnutrition, or underlying tuberculosis; prior administration of steroid hormones; severe anemia; white blood cell count; hemostatic functions; and capillary fragility.

Table 1 lists these diagnostic factors in differential form. It is to be stressed that accurate clinical appraisal is probably not possible in every case. Eight of 68 cases reviewed in preparing this communication could not be classified by use of this table.

Summary

A case of febrile purpura complicating chickenpox is presented.

From a review of the literature of purpuric chickenpox, five separate syndromes are distinguished on the basis of probable etiology, clinical manifestations, therapy, and prognosis:

1. Febrile purpura, a benign and transient form of purpura due to increased capillary fragility resulting from capillary dilatation accompanying fever.

2. Malignant chickenpox with purpura, a frequently fatal syndrome due to overwhelming infection, and manifested by toxicity, central nervous system signs, pneumonia, and hemoptysis, and sometimes precipitated by prior steroid therapy.

3. Postinfectious purpura, characterized by prolonged thrombocytopenia and bleeding for several months, with little constitutional reaction and favorable outcome.

4. Purpura fulminans, a rapidly progressive hemorrhagic gangrene of the extremities of children, accompanied by hemorrhagic shock, and usually fatal.

5. Anaphylactoid (Schönlein-Henoch) purpura, characterized by urticaria, joint or abdominal pains, nephritis, normal platelet count, normal hemostatic functions, and negative Rumpel-Leede test.

Other forms of bleeding complicating varicella are discussed briefly.

Acknowledgments

The following persons made valuable suggestions in the preparation of the manuscript, and their help is gratefully acknowledged: Colonel W. D. Tigertt (MC), Lt. Colonel E. L. Overholt (MC), Captain Aaron G. Meislin (MC), U. S. Army Medical Unit; Dr. Theodore E. Woodward, and Dr. Carroll L. Spurling, University Hospital. Laboratory determinations were performed by the Clinical Laboratory, U. S. Army Medical Unit, Fort Detrick, Maryland.

Summario in Interlingua

Purpura es un complication incommun de varicella. Super le base del differentias de etiologia, del manifestationes clinic, del prognose, e del therapia, cinque major syndromes purpuric pote esser recognoscite.

1. Purpura febril, un forma benigne e transiente causate per le augmentate fragilitate capillar que resulta ab le dilatation capillar associate con febre. Certe subjectos con constitutionalmente basse resistentia capillar es forsan particularmente apte a disveloppar iste syndrome. Purpura febril es probabilemente le complication hemorrhagic le plus commun de varicella. Usualmente illo require nulle tractamento.

2. Varicella maligne con purpura, un frequentemente mortal syndrome causate per un infection fulminante con le virus e distinguite per toxicitate, signos de systema nervose central, pneumonia, e hemoptysis. Su declaration occurre in le precoce phase eruptive, e in recente annos illo ha frequentemente essite precipitate per le antecedente therapia a steroides de un non-relationate morbo.

3. Purpura non-infectiose, que appare usualmente durante le tardive phase eruptive o le precoce phase convalescente e que persiste durante periodos de usque a quatro menses, con thrombocytopenia associate. Como in le caso de purpura febril e de varicella maligne con purpura, le sanguination se face ad in le pelle, le membranas mucose de naso e bucca, e le vias alimentari e urinari. Le reaction constitutional es minime. ACTH pare esser benefic, sed illo non es curative. Le pathogenese es probabilemente illo de un reaction allergic, resultante in un reduction o le absentia complete del formation de plachettas e in injurias vascular.

4. Purpura fulminante, un rapidemente progressive e frequentemente symmetric gangrena hemorrhagic in le extremitates de juveniles, accompaniate de choc hemorrhagic, e a termination usualmente mortal. Hemorrhagia ad in le vias alimentari, respiratori, e urinari es quasi semper absente. Le etiologia es obscur. Le therapia es pauco satisfacente.

5. Purpura anaphylactoide (de Schönlein-Henoch), characterisate per urticaria, dolores articular o abdominal, nephritis, normalitate del numeration plachettal e del functiones hemostatic, e negative tests de fragilitate capillar.

A parte iste cinque syndromes, sanguination pote occurrer durante le curso de varicella como resultato de un gangrena hemorrhagic causate per le colonisation con bacterios pathogene o como le effecto de un non-relationate morbo subjacente, como per exemplo leucemia.

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HEMOPTYSIS CAUSED BY ASPIRATED GLASS FOREIGN BODY *

By Neale Barnes, M.D., James Graham, M.D., and Alan S. Rubenstein, M.D., *Springfield, Illinois*

The present understanding of illness caused by foreign bodies lodged in the air and food passages is due largely to the contributions of Jackson and Jackson.[1] Others have added to the literature as the recognition of this problem has gained momentum, so that now the presence of a foreign body in the bronchus must be considered in the differential diagnosis of a great many pulmonary problems. Illnesses caused by aspirated foreign bodies are unique in their unlimited variation of clinical manifestations and mimicry of other diseases.[1–4] The proper diagnosis is imperative for correct treatment; in few other major pulmonary diseases is the physician offered the opportunity of attaining such a high rate of complete recovery. The present case is reported because its clinical manifestations have not been previously described, nor has this particular kind of foreign body been reported. An apparent cure has been attained.

Case Report

This 15-year-old white female was referred to us on August 13, 1957, two hours after a sudden hemoptysis. She had been entirely well until 18 months before, at which time there had occurred the first of six separate episodes of coughing productive of small quantities of blood. The largest amount of blood was estimated

* Received for publication January 4, 1960.
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to be one tablespoonful. The amount of hemoptysis before admission was estimated to be one pint. The patient denied any other symptoms. There had been no febrile illnesses, no other coughing of any degree, and her physical activities were unlimited. There was no history of any past significant respiratory illness, and there had been no injuries.

The physical examination revealed an alert girl whose blood pressure was 120/70 mm. Hg, pulse, 76, and respiration, 12. On physical examination the only significant findings were a few coarse râles heard over the right lower posterior chest. There was neither evidence of injury nor scars over the trunk. Fluoroscopy and x-ray studies on August 13, 1957, were reported as follows: "Frontal, lateral, and oblique films show no abnormality of the bony thorax, the diaphragm, or the cardiovascular silhouette. Diaphragms move normally at fluoroscopy. A large density is noted at the inferior pole of the right hilum. This extends toward the area of the superior segment of the right lower lobe. Impression: Findings strongly suggest pulmonary tuberculosis, primary type."

Urinalysis, negative; hemoglobin, 12.5 gm.%; hematocrit, 40%; white blood count, 8,500/cu. mm. with a normal differential. Skin testing with both first and second strength PPD gave negative reactions, as did coccidioidin. There was a positive reaction to histoplasmin in 1:100 dilution. During the next few days the patient had no further complaints, and hemoptysis did not recur. Bronchoscopy was performed on August 19, 1957. In the right main stem bronchus on the postero-lateral wall at the level of the middle lobe orifice there was an "area of redness and what appeared to be thickening beneath the epithelium." Repeated examinations

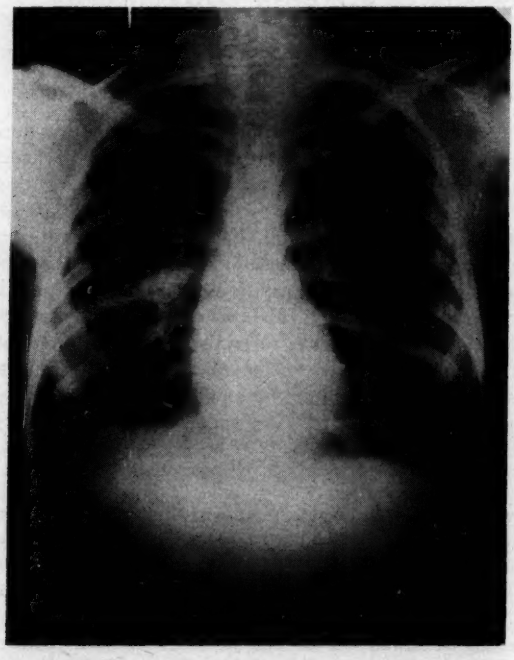

FIG. 1. Posteroanterior chest x-ray, revealing shadow in right mid-lung field.

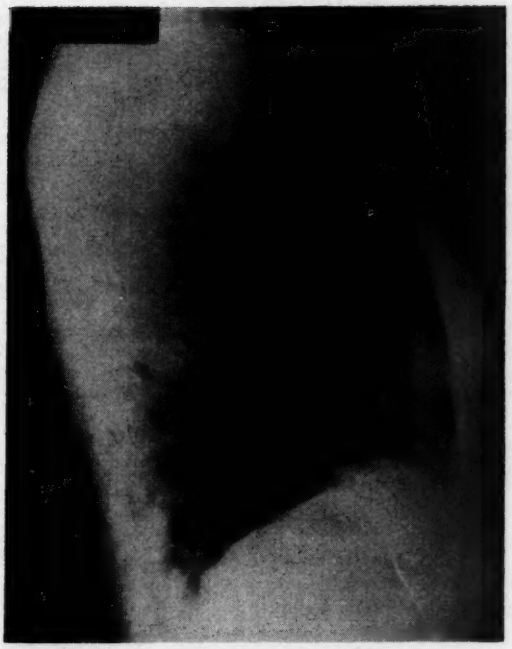

FIG. 2. Right lateral x-ray view, localizing shadow in the superior segment of the right lower lobe.

of sputa, gastric washings, and bronchial washings were negative for acid-fast bacilli on stained concentrates and cultures.

The patient had no further difficulty until January, 1958, after which she experienced occasional bouts of coughing that produced blood-tinged sputum. These occurred as isolated episodes, each separated by from three days to a week. This continued for one month, and during this time x-ray films (Figures 1 and 2) revealed no further change. There were no positive physical findings. Skin testing with PPD remained negative.

The patient remained asymptomatic until May, 1958, when she again coughed up blood-tinged sputum. This was repeated several times, and on May 21, 1958, she experienced another sudden massive hemoptysis while visiting in another city. She was hospitalized immediately, the bleeding ceased, and she returned to us for care on May 23, 1958. At that time she was found to have decreased breath sounds in the right lower posterior chest, but no other positive physical findings. Chest x-rays were the same as before, and the blood counts were similar to those of the last admission. There was no further bleeding. On June 3, 1958, bronchoscopy was again performed. On the right, at the level of the middle lobe orifice, there was "an appearance of narrowing due to granulation tissue."

On June 5, 1958, an angiocardiogram failed to show sufficient opacification of pulmonary vessels for diagnostic purposes, and on June 7, 1958, bronchography revealed "good filling of all bronchopulmonary segments with the singular exception of the superior segment of the right lower lobe. Visualized bronchopulmonary segments are normal in appearance."

On June 10, 1958, right lower lobectomy was performed. It was necessary to remove the entire lobe, due to the anatomy of the pulmonary vasculature found at operation: "The entire superior segment of the right lower lobe was involved in a very dense and firm fibrotic process. The fissure was opened between the middle and lower lobes. This was done with some difficulty because of the intense fibrosis. The hilum of the lower lobe was occupied by large, soft, discrete lymph nodes measuring as large as 1.5 cm." The patient made a rapid and uneventful recovery and was discharged on October 17, 1958. She has remained entirely well to the time of reporting.

Pathology Report: In the superior segment of the lower lobe "there is a mass of tough fibrous tissue." Imbedded in the bronchial wall of the superior segment there was found "an irregular, peculiarly curved fragment of glass," 5 mm. in its longest dimension. Microscopic: Peribronchially, at this location "there is fibrous tissue with chronic inflammatory infiltrates and a focus of polymorphonuclear leukocytes suggesting a small abscess." Unfortunately, the relationship of this fragment to the surrounding vasculature was not described.

Comment

The literature contains excellent comprehensive reviews of intrabronchial foreign bodies and their manifestations.[1-5] These manifestations are influenced by many factors, including size and shape, composition, age of the patient, length of time the foreign body has been retained, and the circumstances under which aspiration has occurred.[6-8] It is superfluous to repeat these excellent reviews of the pathologic physiology.

The larger series of cases are those reported by Jackson and Jackson[1] and Holinger et al.[2] From a combined total of 2,920 cases of intrabronchial foreign body, these two groups did not specify a single instance of an imbedded glass fragment, nor did they specify hemoptysis as a single presenting manifestation. Hemoptysis is not unusual in these problems, but in all instances it appears to accompany a cough productive of mucopurulent sputum.[1] Moore claims hemoptysis to be rare in bronchiectasis except when secondary to a foreign body.[9]

There was no history of aspiration of this fragment, nor was there a history of injury or of the physical findings consistent with penetration through the chest wall. The length of time the fragment had been imbedded is speculative, but it must have been at least 18 months prior to the first visit, and probably longer. Linton et al. have stressed the differences in these problems resulting from foreign bodies recently inhaled, as contrasted to those of long standing.[3] Rarely is a helpful history forthcoming. Linton reports 16 cases, and the time intervals following aspiration vary from six months to nine years. Lewin reports a particle from a pipe stem being recovered from the bronchus after 31 years.[10]

Most writers on this subject have noted that diagnostic problems of this nature are more apt to occur when the aspirated foreign body is radiolucent. However, long-standing pulmonary problems of this kind have been reported in which a well visualized foreign body has been overlooked.[8, 11]

In retrospect, the bronchoscopic appearance in this patient might have suggested the underlying cause. Similar bronchoscopic descriptions have been repeatedly noted by other authors.[1, 2, 7, 9, 12, 13] Whenever possible, the treat-

ment of choice is removal of the foreign body through the bronchoscope. However, when necessary, surgical excision, as dictated by the operative findings, should be performed without delay.

Summary

A case is reported of aspirated foreign body with apparent cure following lobectomy. This case merits attention because the only symptom was hemoptysis, and the offending object, a fragment of glass. Neither of these has been previously reported.

Summario in Interlingua

Es reportate un caso de hemoptysis que es unic in tanto que illo esseva causate per un corpore alien de vitro e se manifestava in tusse con production de sanguine sed nulle mucopurulente sputo a ulle tempore. Iste aspectos non es reportate in ulle del casos in le litteratura.

Le caso re-signala emphaticamente le problemas diagnostic presentate per morbo pulmonar que es causate per radiolucente corpores alien in le bronchos, in le absentia de un antecedente de aspiration. Es revistate le aspectos clinic e bronchoscopic de iste problema. Le frequente absentia de antecedentes de aspiration in casos a corpores alien es notate.

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MYOCARDITIS AND ENCEPHALITIS IN A CASE OF SUSPECTED PSITTACOSIS *

By GORDON J. VOSTI, M.D., *San Jose, California,* and HOWARD ROFFWARG, M.D.,† *New York, N. Y.*

IN recent years, psittacosis has been the subject of many case reports and reviews.[1-5] Its clinical and pathologic variations have been well documented in such standard texts as that of Rivers.[6a] Myocarditis complicating this illness has rarely been reported. We recently observed a case of suspected psittacosis with pneumonitis, encephalitis, and myocarditis, which terminated fatally.

CASE REPORT

A 48-year-old white female was admitted to Stanford University Hospital for the fourth time on September 26, 1958, in a semistuporous state. Previous admissions had been for chronic cervicitis, total hysterectomy and bilateral oöphorectomy for myomata and ovarian cyst, and subtotal thyroidectomy for thyroid adenoma. There was a two-week history of productive cough, shaking chills, bilateral earaches, back pain, substernal aching, and intermittent confusion. Two days prior to admission the patient had been seen in the outpatient department, where a chest x-ray (Figure 1) showed a patchy pneumonitis in the right upper and lower lobes. White blood count was 8,700/cu. mm.; hemoglobin, 13 gm.%. The patient was placed on oxytetracycline, taking two to 10 capsules over the next two days. Three days prior to admission she apparently had had a grand mal seizure, unknown at the time of her outpatient visit, additional seizures on the day of her visit, and several more during the day and evening before admission.

On admission the patient's temperature was 36.5° C. by rectum; pulse, 100/min.; respiration, 28/min.; blood pressure, 150/105 mm. Hg. There was no rash. Her neck was moderately stiff. The ocular fundi were normal. There were decreased breath sounds, dullness, and coarse, sticky inspiratory râles over the right lung field in the scapular area. The heart was not enlarged, and its rhythm was sinus. P-2 was greater than A-2. There was a loud apical presystolic gallop. The liver was not enlarged. Neurologic examination showed some rigidity of the right arm, a positive Babinski's reflex on the right, and slightly increased deep tendon reflexes on the right side.

Laboratory: White blood count, 7,150/cu. mm. (81 mature neutrophils, eight band forms, eight lymphocytes, and three monocytes). Packed cell volume, 41.5%. Hemoglobin, 13.2 gm.%; corrected erythrocyte sedimentation rate, 46 mm./hr. Urinalysis: specific gravity, 1.013; sugar, 1-plus; acetone, trace; white blood cells, 5 to 6; granular casts per high power field, 2 to 3. Serology, negative. Lumbar puncture revealed an opening pressure of 270 mm. of spinal fluid; closing pressure, 180 mm.; the fluid was clear, and contained three red blood cells and no white blood cells/cu. mm. Pandy, 1-plus; protein, 41 mg.%; chloride, 122.9 mEq./L.; sugar, 97 mg.% (blood sugar, 228 mg.%). Spinal fluid cultures were negative, and no fungi were seen. Blood urea, 42 and 23 mg.%; creatinine, 2.2 and 1.2 mg.%; calcium,

* Received for publication February 1, 1960.

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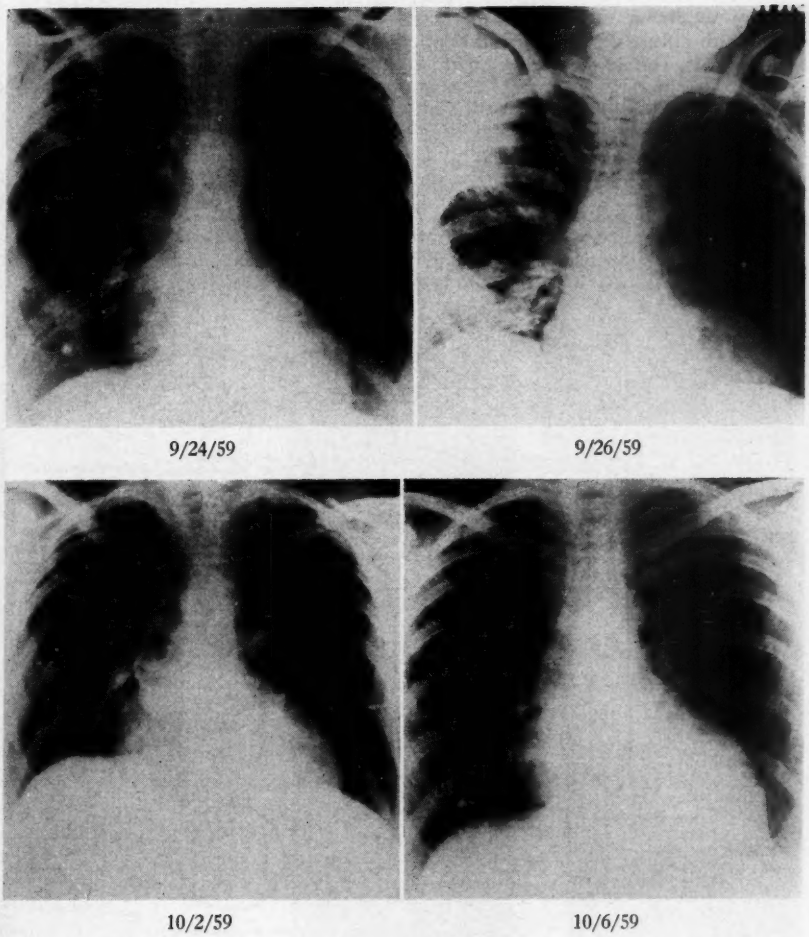

FIG. 1. Patchy right upper lobe and lower lobe pneumonitis, with subsequent clearing.

9.4 mg.%; sodium, 139 mEq./L.; potassium, 4.3 mEq./L.; carbon dioxide, 22.9 mM/L.; chloride, 105 mEq./L. Sputum, nose, and throat cultures were negative. Urine culture showed paracolon bacteria and *Escherichia coli* in small numbers. Two blood cultures were sterile. Cold agglutinins were negative. Cholesterol, 220 mg.%; total protein, 6.3 gm.% (albumin, 3.1 gm.%; globulin, 3.2 gm.%); thymol turbidity, 1 unit; cephalin flocculation, 1-plus in 48 hours. Bromsulfalein retention, 15% and 22% in 45 minutes. Protein bound iodine, 3.5 μg.%. Iodine I^{131} uptake, 32% (normal, 15 to 40%) in 24 hours.

Electroencephalograms (Figure 2) were interpreted as follows:

Day 1: Mild diffuse slowing, with high voltage slow waves and spikes, mostly frontal, with seizure. No lateralization.

Day 4: Severe diffuse abnormal slow activity without convulsive pattern, consistent with diffuse cerebral dysfunction.

Day 11: Hardly borderline, with a little more slow activity than should be present. Greatly improved.

Chest x-rays (Figure 1) were interpreted as showing:

June 22, 1953: Normal chest x-ray.

Two Days Prior to Admission: Probable pneumonitis, anterior segment, right upper lobe and right lower lobe.

Day 3: Slight progression of infiltration in right upper lobe and right lower lobe.

Day 7: General appearance of resolving infiltrative lesions in the right lung, with the appearance of two small areas of atelectasis in the left midlung field.

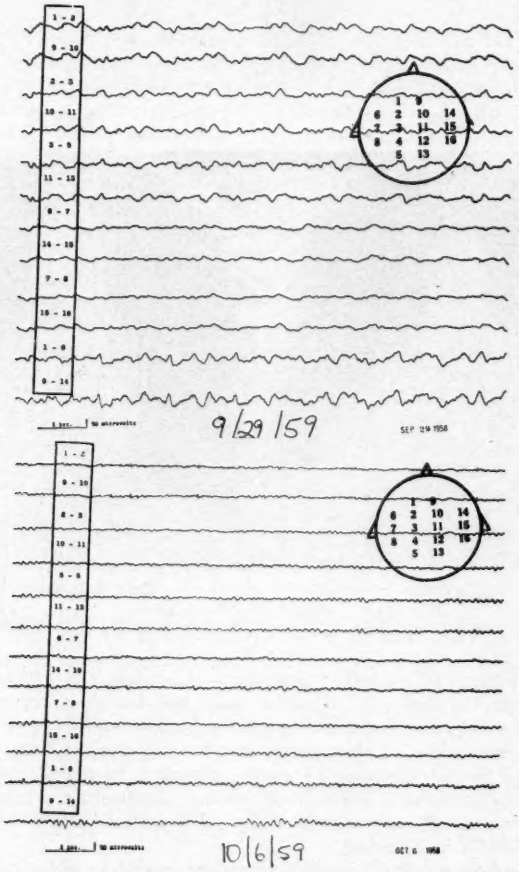

FIG. 2. (Above). Electroencephalogram on 9/26/59, showing severe diffuse abnormal slow activity without convulsive pattern, consistent with diffuse cerebral dysfunction. (Below). Electroencephalogram, greatly improved seven days later.

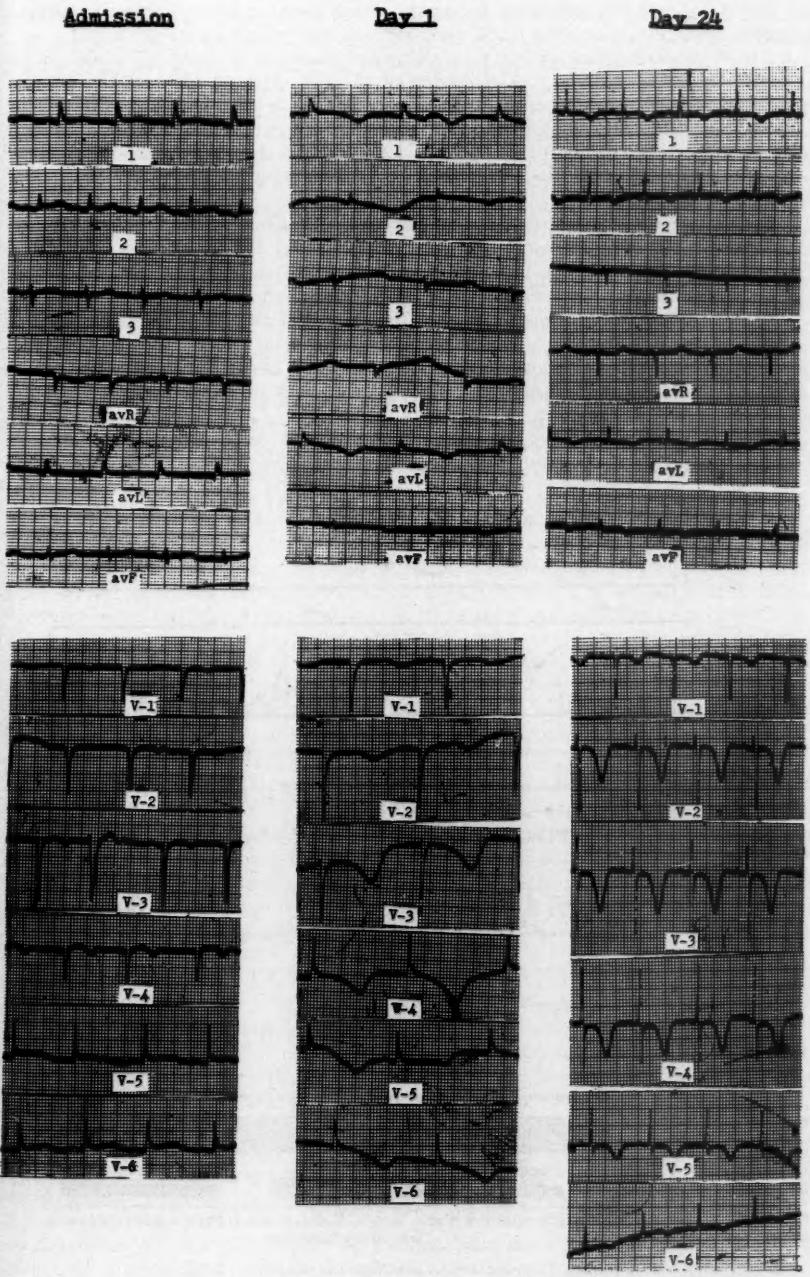

FIG. 3. Electrocardiograms showing striking ST segment prolongation and T wave inversion.

Day 11: Resolving pulmonary infiltrate. Some increase in the transverse cardiac diameter, probably representative of some left ventricle enlargement.

An electrocardiogram (Figure 3) taken on admission revealed ST elevation in Leads I, II, AVL, and V_{4-6}, prolongation of the QT interval (0.4 sec.), absent R waves in Leads V_{1-4}, and a single premature ventricular contraction. By the following day, marked prolongation of the QT interval had occurred (0.8 sec.), along with wide T wave inversion, most striking in Leads V_{3-6}. Multiple follow-up tracings were taken and all were abnormal, showing prolongation of the QT interval and abnormal T waves.

Serum lactic acid dehydrogenase the day following admission was 163 units, rose to a peak of 717 five days later, and slowly dropped to 183 by the eighteenth day. Leukocytes, rising to a peak of 18,000/cu. mm. with a shift to the left, followed a similar pattern except for a terminal rise to 29,000/cu. mm.

Hospital Course (*Figure 4*): Within 10 minutes of admission the patient had a grand mal seizure. Initially her seizures were controlled with parenteral Dilantin. The night of admission she developed hypotension (to a low of 70/60 mm. Hg on one occasion). She did not appear clinically to be in shock at this time, and her pulse was slow.

Over the first four days the patient had frequent periods of unconsciousness, lasting from two to five minutes and alternating with lucid intervals. At other times

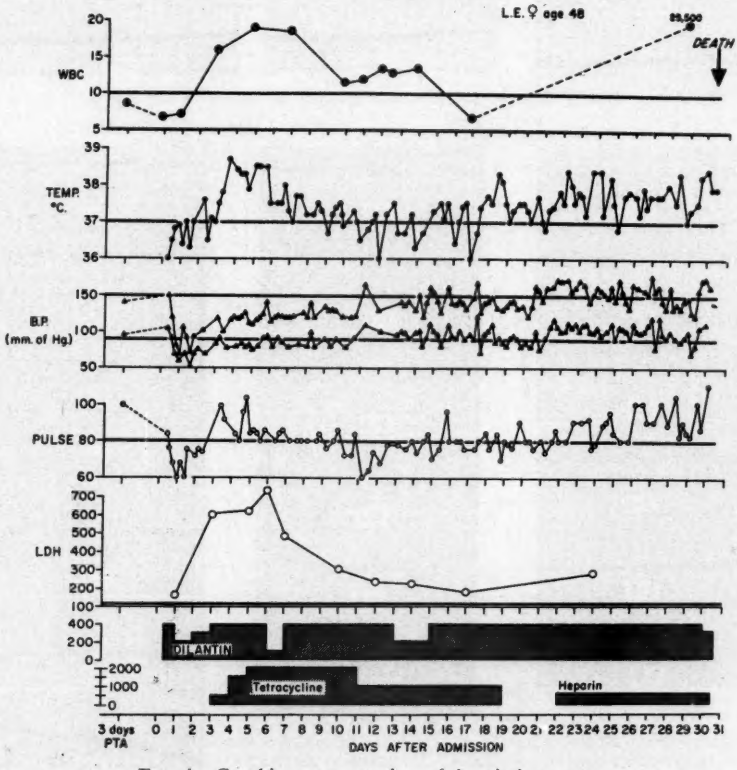

FIG. 4. Graphic representation of hospital course.

she was awake but would not talk or respond to commands. Her speech was occasionally thick, hesitant, and unintelligible. On the day following admission it was discovered that the patient kept several parakeets at home, one of which had died some three weeks previously. A psittacosis complement fixation test was performed at the George Williams Hooper Foundation Laboratory, University of California, which, on the evening of the fourth day, was reported as strongly positive at a dilution of 1:64. Therapy was started with tetracycline at this time and continued for the next 16 days, with a steady drop in titer positivity to 1:16. Complement fixations for Q fever and influenza A and B were negative. The patient's temperature rose to 38.7° C. rectally by the fourth day and returned to normal by the eighth day. There was a low-grade fever during her last 10 days of life.

By the morning of the sixth day the patient was alert and cheerful, able to read the paper, and to comment upon the news. She continued, however, to have some difficulty in speaking and in expressing herself. By the ninth day following admission she was able to sit up in a chair, and by the eleventh day was removed from isolation. She had a transient bout with nausea, vomiting, and diarrhea on the twelfth day. Some stuttering was noted 15 days after admission. Liver biopsy performed on the twentieth day showed mild, subacute portal inflammation. She had difficulty in speaking on the twenty-first day, and then had an episode of throwing food on the floor and responding only with a "silly" grin. The following day she was semicomatose, and there was evidence of a right hemiplegia, with flaccid paralysis, right facial paralysis, aphasia, and a cold, pulseless right foot. It was felt that she had had multiple emboli originating in the left ventricle of her heart. A lumbar puncture revealed an opening pressure of 180 mm. of spinal fluid, with a closing pressure of 120 mm. No cells were seen; protein, 50 mg.%; chloride, 128.6 mEq./L. Cultures were sterile. Anticoagulation with heparin and tube feedings were instituted. Over the next six days there was some return of deep tendon reflexes on the right side, and the patient could be aroused and would obey commands. Her right side was still flaccid, and bilateral Babinski's reflexes were present. Thirty-one days after admission the patient was noted to be hyperpneic, and there was some abdominal distention. Her pulse became rapid and her blood pressure fell. She became pale and sweaty, and died that evening.

Virus Studies: (Performed by The George Williams Hooper Foundation Laboratory, University of California.) Six parakeets were obtained from the home of the patient. Another bird had died and was not available for study. Of the six, one was positive for psittacosis virus by mouse inoculation.

Specimens of the patient's sputum, blood, spinal fluid, and urine obtained on the first and second days of hospitalization were negative for psittacosis virus on repeated mouse passages. Several post-mortem specimens, including lung, heart, and brain tissue, were also negative.

Autopsy: The heart weighed 270 gm. There were 20 ml. of clear fluid in the pericardial cavity. The pericardium and epicardium appeared to be normal. The coronary arteries showed mild arteriosclerosis. The valves were normal. Within the left ventricle, over the distal portion of the interventricular septum near the posterior ventricular wall, were two rounded, pedunculated, friable thrombi, 8 mm. and 5 mm. in diameter, adherent to the endocardium (Figure 5). No underlying endocardial or myocardial lesions were evident. Multiple sections from the left ventricle examined histologically showed scattered small foci of fibrosis throughout the myocardium; some appeared to be quite old, others showed considerable numbers of fibroblasts, lymphocytes, and brown-pigmented macrophages. A few similar foci were seen in the right ventricle. Some of these small lesions were in the subendocardium, but the subadjacent myocardium was not remarkable except for mild, irregular atrophy and occasional loss of striation. The left ventricle contained

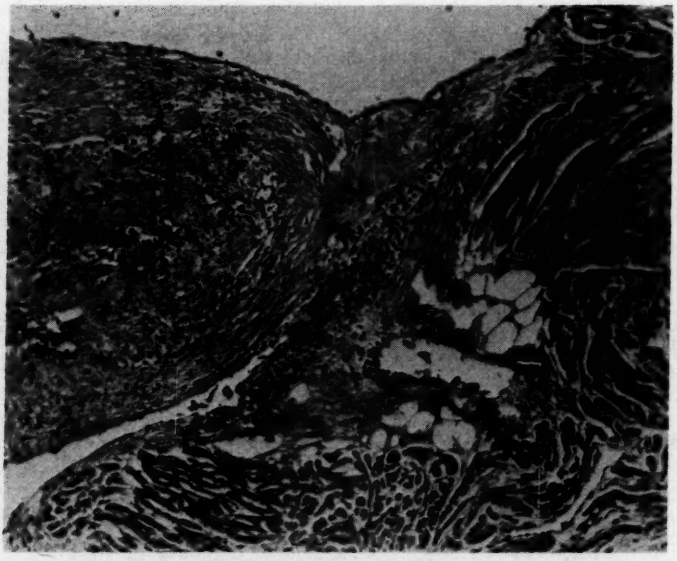

FIG. 5. Organization of mural thrombus and attachment to wall of left ventricle. (H & E, magnification approximately 150 ×.)

a single 0.5 cm. lesion, which showed disappearance of muscle, with replacement by loose collagenous tissue, small engorged vessels, a few lymphocytes, polymorphonuclear leukocytes, and macrophages. One of the mural thrombi was sectioned and microscopically showed a mottled degenerating thrombus with a zone of organization (Figure 5).

The lungs were slightly heavy and were of an unusual greyish brown color, particularly in the posterior portions. No thrombi were found in the arteries or veins. There was no gross evidence of pneumonia. Histologically, the alveolar walls throughout showed minimal to moderate edema, and generally moderate engorgement of capillaries with polymorphonuclear leukocytes. Only a few small zones of septal cell hyperplasia and/or mild hyaline plaque formation were seen, with small numbers of lymphocytes and macrophages in some alveoli. Multiple systemic arteries contained emboli, with infarction of the entire left kidney, portions of the right kidney, jejunum, liver, pancreas, spleen, and brain. Emboli in the celiac axis and in the hepatic and left midcerebral arteries showed advanced central degeneration and minimal peripheral fibroblastic invasion, while those in the left renal artery showed extensive peripheral organization. Except for the areas of infarction, the gastrointestinal tract was unremarkable, though the liver showed a very few scattered areas of mild subacute inflammation. Similarly, the genitourinary system was unremarkable except for the infarcted areas and a mild cystitis and urethritis. The spleen contained an infarct but was otherwise unremarkable. Also unremarkable were the bone marrow, pituitary and adrenal glands, the remaining thyroid tissue, skeletal muscle, skin, and breasts. The brain, grossly and microscopically, showed massive recent infarction of the area supplied by the left middle cerebral artery, focal areas of degeneration in the right occipital cortex and cerebellum, questionable scattered loss of nerve cells in the cortex of the right cerebral hemisphere, perivascular deposits of "pseudocalcium" in the basal ganglia, and congestion of vessels. Minimal

lymphocytic perivascular cuffing was noted. A rather heavy cellular infiltration of mononuclear cells (histiocytes, lymphocytes, and occasional plasma cells) was seen in the vicinity of the sylvian fissure. None of the lesions in the infarcted area appeared to be older than nine to 10 days.

Careful search of specially stained sections from lung, heart, liver, and brain failed to reveal the presence of intracytoplasmic bodies of psittacosis.

Discussion

The diagnosis of psittacosis in this case is supported by the following points. The patient had been exposed to birds proved to have the infection, one of which had recently died. Her clinical picture was consistent with this infection. The initial complement fixation titer was high (strongly positive, 1:64), which, in itself, is generally presumed to be evidence of recent infection.[6] Meyer and Eddie have stated that a serum titer of 1:16, when obtained from a patient with clinical manifestations suggestive of psittacosis, may be considered to be positive.[7] After three weeks of intensive tetracycline therapy, our patient's serum showed a two-tube fall to a positive titer of 1:16. There seem to be meager data in the literature relative to this last point, namely, a high titer falling in a short time in response to intensive tetracycline therapy. A case is known to us of a patient who had a titer of 1:20 on day 13 and of 1:40 on day 18, and a negative reaction on the twenty-fifth day.[8] This patient had received Aureomycin for seven days. An additional case, from the same source and also treated with Aureomycin, showed a drop in titer from 1:20 on the twenty-first day of illness to 1:10 on the twenty-eighth day. Both of these were laboratory-acquired infections. The failure to isolate the virus in our case, though unfortunate, was not unexpected, because of the treatment with oxytetracycline before admission.

A severe cardiac lesion in this case was manifested clinically by gallop rhythm, hypotension, elevation of lactic acid dehydrogenase, and marked electrocardiographic abnormalities. Serum elevation of lactic acid dehydrogenase, while occurring with tissue damage in liver, kidneys, skeletal muscle, brain, and certain tumors,[9] seemed best correlated here with myocardial damage. The liver at biopsy and autopsy failed to show evidence of significant hepatitis. The bromsulfalein retention was abnormal, and thus hepatic damage cannot be absolutely excluded, though at a time when the lactic acid dehydrogenase was very high (600 units) the isocitric dehydrogenase was only slightly elevated (360; normal, 50 to 288). Wróblewski states that spinal fluid enzyme studies are for the most part uninfluenced by serum enzyme alterations, and vice versa.[10] It is thus unlikely that brain damage caused the serum enzyme alteration. Although at autopsy one kidney was found to be totally infarcted, the time sequence is not consistent so as to implicate this.

In the absence of hypocalcemia, hypopotassemia, or quinidine toxicity, the markedly prolonged QT interval with T wave abnormalities must have been on the basis of metabolic derangements occurring with myocardial damage caused by anoxia, an unknown toxin, or an infectious agent. The electrocardiographic abnormalities were not those of the usual subendocardial infarction. There was no significant coronary artery disease. Pathologically, the

findings were most compatible with an almost completely healed myocarditis, about six weeks old.

Myocarditis has been found to be an occasional complication of a great many infectious diseases.[11-13] This diagnosis has been supported by clinical, electrocardiographic, and anatomic evidence when available. Most standard texts of cardiology mention "virus disease" or "virus pneumonia" as being implicated in the etiology of occasional cases of myocarditis. However, none has specifically mentioned psittacosis.

Of the numerous articles on psittacosis in the literature, few stress myocarditis, per se, as a significant complication. Death from psittacosis has been attributed in the early stages of illness (seven to 15 days) to pneumonic involvement, or later to loosening of a complicating venous thrombosis.[14] Autopsy material reported in the literature has been interpreted variously as showing: no sign of importance in the heart;[15] parenchymatous degeneration of myocardium, liver, and kidneys;[16] edematous myocardium with hemorrhagic areas in endocardium of mitral, tricuspid, and aortic leaflets, with swelling of muscle cells throughout and discrete foci of polymorphonuclear leukocytes and plasma cell infiltration between muscle cells;[17] a single subepicardial hemorrhage 0.3 cm. in diameter but otherwise normal;[2] interstitial myocarditis, especially of the right heart and mainly of the right auricle, and some myolysis.[18] Lyon has reviewed some of these data in his excellent monograph.[19]

A case recently reported by Jannach of an 18-month-old female infant who died from "idiopathic myocarditis" is of great interest.[20] The psittacosis virus was isolated by mouse inoculation from birds kept in the child's home. At autopsy, characteristic inclusion bodies were found in the heart, lung, and liver of the infant which were exactly the same as those obtained from the birds. Unfortunately, no complement fixation test had been done prior to death.

In nonfatal cases there have been several reports of clinical and electrocardiographic evidence suggesting myocarditis.[21-24] Although it must be understood that many cases of this disease have been reported with no clinical or electrocardiographic findings to suggest myocardial involvement, there are many reports in the literature where no electrocardiograms were available or reported. The actual incidence of clinically significant involvement of the heart by this virus would seem to be small. But, as is the case with many other virus illnesses that have been more completely studied in recent years, myocardial involvements may be much more common than has been suspected.

The encephalitic manifestations of psittacosis are well known. Only rarely is a case reported in the literature without mention of severe headache, restlessness, or stupor. Often there are delirium and meningeal signs, and occasionally there are focal neurologic signs of a transient nature.[25-31] Our patient showed these changes but, in addition, presented with grand mal convulsions and was in status epilepticus. She gave no previous history of seizures. Convulsions have never been reported as part of the clinical picture of infection with the psittacosis virus. However, Museteanu et al.[32] reported them in children infected with a virus showing many characteristics of the psittacosis-lymphogranuloma venereum group,[33] and they have been observed in patients who contracted laboratory infections with toxic strains of psittacosis virus.[34]

Analysis of the electroencephalograms points to a generalized cerebral in-

volvement of an extremely severe nature, but the electrical abnormalities had virtually cleared by the tenth hospital day. Despite an obviously acute central nervous system involvement, the cerebrospinal fluid never showed an elevated protein or a cellular reaction.

The question might be raised whether unsuspected multiple cerebral emboli could have been responsible for the initial convulsions and encephalopathy. The clinical picture and the electroencephalographic data, however, suggest a diffuse cerebral malfunction of a magnitude that can be explained only on a toxic or an infectious basis. The encephalitis in this case must be accepted as part of the infection. In the few cases reported in the literature where spinal fluid examination has been undertaken, the protein content has been normal or slightly elevated, and no more than two to three white blood cells per cubic millimeter have been found.[1, 25, 27] Pressure may or may not be elevated. No electroencephalograms were done in the cases reported in the literature.

The brain showed very little to document a viral disease. The predominant finding was a 5 by 5 cm. area in the left hemisphere in the distribution of the middle cerebral artery in which an embolus was lodged. There were two other small areas of focal degeneration, and a questionable scattered loss of nerve cells in the right cerebral cortex. These were the changes of recent cerebral embolus with infarction. However, the mononuclear exudate observed in the meninges in the area of the sylvian fissure, the focal areas of cortical congestion, minimal lymphocytic perivascular cuffing, and the yellowish brown deposits in the basal ganglia were interpreted as subtle residues of an older, resolving meningoencephalitis.

The pathologic changes in the central nervous system in the cases of psittacosis noted in the literature are relatively nonspecific. Lillie in 1933 reviewed all of the autopsy data collected to that time and concluded that the principal findings were "meningeal and cerebral congestion and perivascular hemorrhages in the brain and cord."[35] Others supported this contention.[29, 36, 37] Some workers, however, found lymphocytic infiltrations and perivascular round cells or pigment cells.[17, 29, 30, 38] Proliferation of glial elements was also observed in scattered locations.[17, 30] Increased quantities of fat were found in the anterior horn cells and in the macrophages.[30] Polayes and Lederer[17] found moderate tigrolysis and gliosis and rusty pigmentation of the basal ganglia, along with nerve cell swelling; they examined the cord carefully in one case and found small hemorrhages in the anterior horns. A few workers have noted a gelatinous exudate containing mononuclear cells covering the meninges, and Walton in 1954 was able to demonstrate intracytoplasmic inclusion bodies (Levinthal-Coles-Lillie bodies) in them in one instance.[39] All of these observations illustrate the diffuse neurologic damage caused by the psittacosis virus in certain cases.

We would like to emphasize that psittacosis should be considered in the differential diagnosis of convulsive or nonconvulsive encephalitis, especially if pneumonia and myocardial aberrations are also in evidence. The electroencephalogram can be expected to show severe but generalized involvement. The cerebrospinal fluid will probably be wholly unremarkable. An attempt should be made to culture the virus from the cerebrospinal fluid as well as from the blood and sputum before therapy is instituted.

Conclusion

A case of suspected psittacosis with pneumonitis, myocarditis, and encephalitis is presented. Severe myocardial involvement was recognized clinically by the presence of gallop rhythm, hypotension, elevation of lactic acid dehydrogenase, and marked electrocardiographic abnormalities. Encephalitis was manifested by delirium, stupor, meningeal signs, seizures, and diffusely abnormal electroencephalograms. Autopsy findings a month later showed little residua of pneumonitis, myocarditis, or encephalitis, but demonstrated multiple organ involvement by emboli from mural thrombi in the left ventricle. This is an unusual complication of psittacosis, apparently adequately treated with tetracycline.

Acknowledgments

The authors wish to thank Dr. David A. Rytand, Dr. Karl F. Meyer, and Dr. Glen B. Haydon for their advice and criticism in the preparation of this paper.

Summario in Interlingua

Es presentate un caso de suspicion de psittacosis con pneumonitis, myocarditis, e encephalitis. Le patiente esseva un femina de racia blanc de 48 annos de etate qui esseva admittite al Hospital del Universitate Stanford a causa de attaccos de grand mal.

Sever morbo myocardial esseva recognoscite clinicamente per le presentia de rhythmo de galopo, hypotension, elevation del nivello de dishydrogenase de acido lactic, e marcate anormalitates electrocardiographic. Encephalitis esseva manifeste per delirio, stupor, signos meningee, convulsiones, e diffusemente anormal electroencephalogrammas.

Le diagnose de psittacosis esseva basate super un historia de exposition a aves inficite (un del quales habeva morite recentemente), super le isolation de virus de psittacosis ab un altere ave in le mesme gruppo, e super le constatation de un alte titro initial de fixation de complemento de psittacosis. Un tal titro, sin altere corroboration, es considerate per certe autores—si illo es incontrate in le appropriate milieu clinic—como diagnostic pro le morbo.

Le patiente esseva tractate con tetracyclina durante 16 dies e con Dilantina durante le integre curso de su hospitalisation. Le vinti-tertie die de su hospitalisation illa disveloppava hemiplegia dextere, con frigor e absentia de pulso in le pede dextere. Su condition se deteriorava lentemente. Illa moriva 31 dies post su admission al hospital.

Le necropsia revelava pauc residuos de pneumonitis, myocarditis, o encephalitis, sed illo monstrava le presentia in multe organos de embolos ab thrombos mural in le ventriculo sinistre. Nulle virus de psittacosis esseva isolate ab le specimens necroptic.

Iste caso illustra un complication inusual de psittacosis. Il pare que illo es tractate adequatemente con tetracyclina.

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WHIPPLE'S INTESTINAL LIPODYSTROPHY *

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In 1907 Whipple described a disease in a 36-year-old physician which was characterized by steatorrhea, weakness, loss of weight, anemia, polyarthritis, and cough.[1] At post-mortem the most striking finding was a massive deposition of fat in the intestinal and mesenteric lymphatic tissues. Whipple named this disease "intestinal lipodystrophy." At this writing, 87 cases have been reported in the world literature, 69 of which fulfill all of the pathologic criteria. In a recent review, Farnan tabulated the salient clinical features in 60 well documented cases, and added seven more from Great Britain.[2] He found that diarrhea, arthritis, and abdominal pain were the most common presenting complaints.

The case described here presents several unusual clinical features. Arthritis and recurrent fevers constituted the major symptomatology for more than 13 years; at no time was there clinical evidence of intestinal malabsorption. The diagnosis was finally made at laparotomy, which was performed because of the finding of a mass in the abdomen.

Case Report

A 46-year-old male was first seen in 1947, at which time he complained of generalized joint pains of 18 months' duration. The neck, low back, wrists, fingers, shoulders, and ankles were involved, but the pain rarely persisted for longer than two or three days in any one joint. He had observed puffiness of the dorsum of the hands and diffuse swelling of the fingers, without heat or redness; intermittent fever (101° to 102° F.); night sweats; an eight-pound weight loss, and increasing fatigue.

* Received for publication February 12, 1960.
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The fevers lasted an average of from five to seven days, and were followed by afebrile periods of weeks or months, with no regularity.

System review revealed that the patient had always been in good health. He had never been outside of the United States, and there had been no exposure to toxic substances in the course of his work in a shipping department. He did not drink or smoke, and had taken no drugs prior to the onset of his illness; specifically, he had never used mineral oil or nose drops. His appetite was normal except during the periods of fever, and there had been no nausea, vomiting, or abdominal pain, though he suffered from chronic constipation which had become somewhat more severe since the present illness began. Family history is perhaps of significance in that his father died at the age of 50 of "colitis."

Physical examination showed the patient to be fairly well developed, well nourished, and alert, though appearing to be chronically ill. Vital signs were normal. There was no abnormal pigmentation and no lymphadenopathy. Examination of the heart, lungs, and abdomen was negative. There was soft tissue puffiness of the left wrist and fingers, but no heat, redness, or deformities were noted. The range of motion of all joints was normal, as was muscle strength. Both ankles showed a similar puffiness, but there was no pitting edema. There was tenderness on direct pressure in the right ankle and heel. Neurologic examination was within normal limits.

Initial laboratory studies gave the following results: hemoglobin, 12.6 gm.; white blood cell count, 12,300/cu. mm., with a normal differential; urinalysis, negative; erythrocyte sedimentation rate (Westergren), 54 mm./hr.; serum uric acid, 5.5 mg.%. Agglutination tests for *Proteus,* typhoid, paratyphoid, *Brucella,* and rickettsiae were negative. X-rays of the chest and peripheral joints showed no abnormalities. An electrocardiogram revealed left axis deviation. A tuberculin skin test was positive.

In September, 1947, a course of intramuscular gold therapy (Solganal B) was begun and was well tolerated, with a total of 1.5 gm. administered by May, 1948. There was no significant change in the patient's course, however; the recurrent fevers and migratory polyarthritis were not favorably influenced by the therapy. During this period, white blood counts varied from 12,000 to 15,000/cu. mm., with normal differentials, and the erythrocyte sedimentation rate remained elevated at 60 mm./hr.

By October, 1948, after the gold had been discontinued, it was decided to treat a febrile episode empirically with intramuscular penicillin in a dose of 600,000 units daily. After five days the temperature became normal. The patient felt strongly that the penicillin had helped to abort his fever, and he requested that the drug be given for subsequent attacks. Those who observed him at the time could not be convinced of a definite therapeutic effect, but it was felt worth while to utilize the antibiotic for the more severe febrile episodes. From November, 1948, to February, 1954, 20 courses of penicillin (seven to 14 days per course) were given. Salicylates were of some benefit in controlling the low grade fevers, and also in alleviating the arthralgias.

In February, 1954, the patient consulted another physician who, after an extensive diagnostic evaluation, was unable to arrive at a definitive diagnosis. He administered 100 mg. of cortisone for a temperature of 104° F. and noted a lysis of the fever within 24 hours. He then placed the patient on maintenance cortisone therapy of 75 mg. daily for one month. There was no fever during the treatment period, but the patient lost 20 pounds and the drug was gradually withdrawn, without an immediate exacerbation of fever. Bone marrow examination, numerous L.E. cell preparations, and multiple blood cultures were all negative. Once again, penicillin was given for treatment of the febrile episodes.

In June, 1956, the patient was admitted to a local hospital because of severe abdominal pain, nausea, and vomiting. An appendectomy was performed, but no

exploration of the abdominal cavity was carried out. The appendix was found to be acutely inflamed, but the appendectomy had no effect on the underlying illness, and the pattern of recurrent fever and polyarthritis continued unchanged.

In June, 1959, the patient experienced increased constipation and bloating and, for the first time, left-sided abdominal pain. On physical examination the temperature was normal, and the only noteworthy finding was abdominal tenderness localized to the left lower quadrant. After a cathartic and an enema, the symptoms disappeared for several weeks, but gradually the abdominal pain returned. A barium enema, gastrointestinal series, and gall-bladder series were performed, with negative results. The patient was placed on a bland, low-residue diet and antispasmodics, but the symptoms persisted. In addition to abdominal pain and distention, he also experienced anorexia, nausea, and weakness. Three months later, on August 13, 1959, he was admitted to the hospital for further studies and evaluation.

Physical findings on admission were as follows: temperature, 99.2° F.; pulse, 90/min.; blood pressure, 110/70 mm. Hg; respiration, 20/min. He appeared to be fairly well nourished and alert, though he showed evidence of recent weight loss. There was no abnormal pigmentation. The head, eyes, ears, nose, and throat were all normal, and there was no pigmentation of the oral mucosa. The trachea was in the midline, the thyroid was not enlarged, and there was no lymphadenopathy. Examination of the heart and lungs was negative. The abdomen was distended and tympanitic. In the left lower quadrant a mass was palpable. Its borders could not be clearly defined, but by ballottement it appeared to occupy the upper two-thirds of the left lower quadrant. It was tender to moderately deep palpation, and there was voluntary guarding of the area. The liver was palpable 2 cm. below the right costal margin, but it was smooth and nontender. The spleen and kidneys could not be felt. A small incisional hernia was present in the appendectomy scar. Rectal and sigmoidoscopic examinations were negative. The extremities showed no evidence of acute or chronic joint disease. There was no clubbing, cyanosis, or edema, and the neurologic examination was negative.

Laboratory studies on admission were as follows: hemoglobin, 13 gm.; white blood cell count, 9,000/cu. mm., with a normal differential. Urinalysis, serology, and stool for occult blood were negative. The erythrocyte sedimentation rate (Wintrobe) was 31 mm./hr. Fasting blood sugar, 75 mg.%; serum glutamic oxalacetic transaminase (SGO-T), 30 units; serum glutamic pyruvic transaminase (SGP-T), 32 units; serum amylase, 106 Somogyi units; alkaline phosphatase, 2.4 Bodansky units; total cholesterol, 139 mg.%; total serum protein, 6.1 gm. By electrophoresis, there were 2.74 gm. albumin, 1.09 gm. beta globulin, and 1.48 gm. gamma globulin. Electrocardiogram and chest x-ray were normal.

On the third hospital day the patient's temperature rose to 101.8° F., and reached a peak of 104° F. within 48 hours. Over the next four days it slowly fell to normal, on no therapy other than salicylates. There was no change in the physical findings to account for the fever, and multiple blood cultures were negative. An intravenous pyelogram was performed in an attempt to delineate further the abdominal mass. It showed anterolateral deviation of the left ureter at the level of L_4, and an obliteration of the psoas shadow on the left (Figure 1). Renal function was normal, with no evidence of obstruction. It was felt that these findings were compatible with a retroperitoneal mass. A laparotomy was performed on the twelfth hospital day, and the following is a summary of the salient operative findings.

The most striking observation on entry into the peritoneal cavity was the prominence of the small bowel mesentery, which was remarkably thickened and distorted by a yellow, nodular, indurated mass of tissue. This was seen to extend into the root of the mesentery from the ligament of Treitz to the ileocecal valve. The process was most prominent in the mesentery of the jejunum, where the consistency

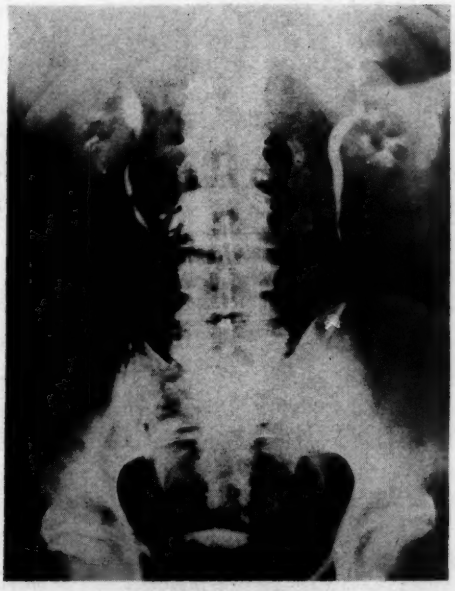

FIG. 1. Intravenous pyelogram, showing anterolateral displacement of the left ureter at the level of the fourth lumbar vertebra. Note the suggestion of a mass overlying the psoas shadow on the left side.

of the abnormal tissue varied from moderately soft to firm. The mesenteric lymph nodes, which were replaced by what appeared to be fat, were enlarged up to 6 cm. in length and were arranged in clusters. In some areas they appeared to coalesce into large, confluent, fatty masses. The small intestine itself was thickened and rubbery to the touch, and had dilated lacteals on the surface, which extended down into the mesentery. The lacteals were most prominent in those areas where the mesentery was most distorted with clusters of enlarged lymph nodes.

Several lymph nodes and a portion of the abnormal mesenteric tissue were removed for biopsy. Frozen sections of representative portions of these tissues revealed large fat spaces and many granulomata with foreign body giant cells. A provisional diagnosis of Whipple's disease was made, and detailed exploration of the remainder of the gastrointestinal tract revealed no other abnormalities.

Following are the results of the pathologic studies.* All of the nodes had identical morphologic characteristics, and the description of a node in the fresh state follows: the node measured 6 cm. in length and 2.5 cm in width. It was an ovoid piece of bright yellow tissue covered by an adherent, diaphanous capsule. Cut section revealed it to be finely granular and yellow, and to have the general appearance of fat.

Biopsy material taken from the confluent masses in the mesentery had a similar color and consistency. Microscopic examination of a lymph node (Figure 2) revealed a loss of the normal architecture. There were large, empty fat spaces, surrounded by many multinucleated foreign body giant cells. Elsewhere there were broad zones of macrophages, or foam cells, which had a pink, finely vacuolated

* Performed by Dr. Marianne Wolff.

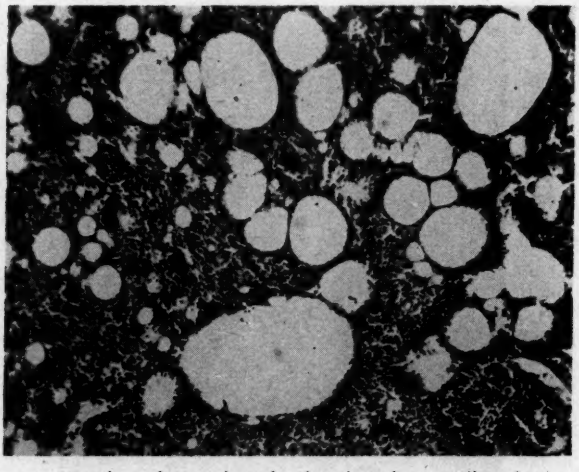

FIG. 2. Medium power view of a section of a lymph node, revealing the large fat spaces, disruption of normal architecture, and multiple areas of granuloma formation. (H & E).

cytoplasm. There were foci of necrosis with infiltration of polymorphonuclear leukocytes. Sections of the mesenteric fat revealed a partial replacement of fat by fibrous tissue, with evidence of actively proliferating fibroblasts (Figure 3). In addition, there was an infiltration of lymphocytes, eosinophils, and macrophages. The granulomatous lesions were composed of central large fat vacuoles, which were surrounded by macrophages. Special stains for fat revealed fat-positive material in the large spaces and, to a lesser degree, within some of the larger macrophages and giant cells. A periodic-acid-Schiff stain for glycoprotein showed the presence of

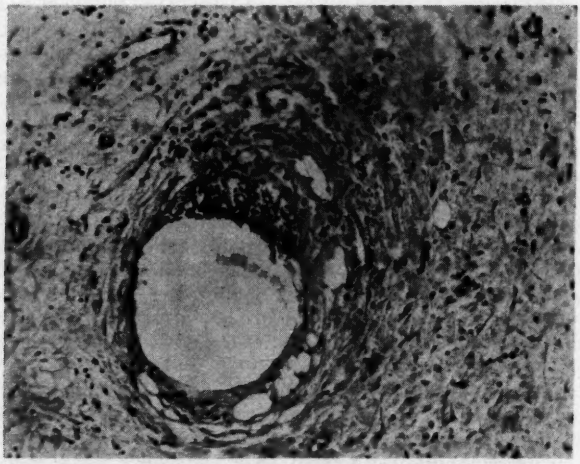

FIG. 3. Section of mesenteric fat, showing granulomatous inflammation surrounding a large fat space. Note the young, rapidly proliferating fibroblasts at the periphery of the lesion. There is considerable replacement of fat by fibrous tissue.

strongly positive para-aminosalicylic acid (PAS) material within the finely vacuolated macrophages. High power view of these cells and the foreign body giant cells revealed the characteristic sickle form aggregates of PAS-positive material (Sieracki bodies) (Figure 4).

The patient was discharged with the diagnosis of Whipple's intestinal lipodystrophy, and was readmitted one month later for further studies. An x-ray examination of the small intestine showed decreased motility and delayed transit time, and an increase in the size of the lumen of the jejunum. There were thickening of the mucosal folds and flocculation of the barium, though not so marked as might be expected in a classic malabsorption syndrome (Figure 5).

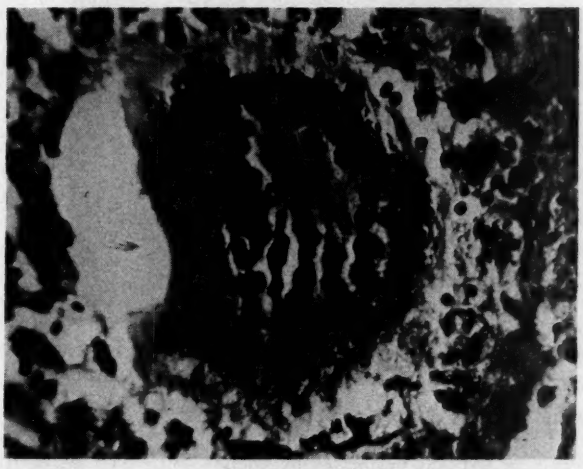

FIG. 4. High power view of multinucleate foreign body giant cell, PAS stain. Black areas represent PAS-positive material which has the appearance of sickle-shaped particles (Sieracki bodies) within the giant cell. Note smaller macrophages at the periphery, containing discrete particles and confluent masses of PAS-positive material.

Serum electrolytes and liver function tests were within normal limits. The serum mucoprotein was 108 mg.% (normal, 40 to 80 mg.%). A standard oral glucose tolerance test gave the following result:

Fasting	90 mg.%
½ hr.	155 mg.%
1 hr.	165 mg.%
2 hrs.	125 mg.%
3 hrs.	100 mg.%

A vitamin A tolerance test was performed with the administration of 6,000 U.S.P. units of vitamin A per pound of body weight. Values obtained are expressed in μg.%

Time	Result	Mean Normal
Fasting	40	37
3 hrs.	76	281
6 hrs.	202	212
9 hrs.	296	134

The quantitative fecal fat content of a 48-hour stool collection was 15% (normal, less than 10%).

FIG. 5. X-ray of the small intestine, showing thickened mucosal folds and minimal flocculation of the barium. Transit time was markedly delayed.

A Schilling test was normal, with 18.6% cobalt^{60}-labeled vitamin B_{12} excreted in 24 hours.

An I^{131} triolein test was performed by administering 34.5 μc. of triolein-I^{131} in the fasting state, and determining the percentage patient dose in the blood hourly for six hours.

Specimen	% Patient Dose in Blood
#4	4.80
#5	5.63
#6	5.83

Average percentage patient dose in blood for hours 4, 5, and 6: 5.4. Normal results are either 12% or more of the patient dose in the blood at six hours,[3, 4] or the average of specimens 4, 5, and 6 over 8%, with less than 5% representing markedly impaired absorption of the triolein-I^{131}.[5, 6]

Following the completion of these studies, the patient was placed on adrenal steroid therapy with 6-methylprednisolone (Medrol) in a dosage of 4 mg. twice daily. After 90 days of treatment he reported an increase in appetite and well being, a gain of nine pounds in weight, a definite decrease in abdominal fullness and pain, and complete freedom from arthritic symptoms. There were two episodes of fever to 102° F., but in both instances there was a spontaneous subsidence of fever within 24 hours, a different pattern from that heretofore observed. He also developed marked cushingoid facial changes and epigastric burning, and requested that the drug be stopped. This was accomplished gradually over a period of seven days, and within 24 hours of the last dose his temperature rose to 104° F. The patient refused to resume the steroid, and insisted on penicillin therapy, which was given for 14 days without benefit. Because of the persistently high fever, anorexia, and a return of

abdominal pain, bloating, and weakness, the steroid was resumed in the previous dosage, and all symptoms promptly remitted. At this writing the patient is on a maintenance dose of 6 mg. daily, and is essentially asymptomatic save for the aforementioned side effects of the drug.

Discussion

Since Whipple first described intestinal lipodystrophy, the clinical and pathologic features have been further clarified. It has been shown that the diagnosis can be reasonably suspected on the basis of the clinical picture alone.[7] In general, the disease has been found most commonly in middle-aged white males who have diarrhea and symptoms of a malabsorption syndrome, loss of weight, and a chronic, nondeforming polyarthritis. Less often, cough, polyserositis, asthenia, pigmentation, lymphadenopathy, and fever are found. Constipation, with or without the subsequent development of steatorrhea, has been noted in 22% of the reported cases.[2] In view of the multiplicity and variety of clinical features, and the small number of cases reported, the complete disease spectrum has not yet been established, and definitive diagnosis depends upon characteristic pathologic findings.

The case here reported had been a diagnostic problem for many years. Early in the illness a diagnosis of rheumatoid arthritis seemed reasonable, but as time passed the recurrent, migratory nature of the joint disease and the lack of characteristic rheumatoid deformities made this less tenable. Furthermore, the peculiar, intermittent, febrile episodes were felt to be related to the articular process, which would also militate against this being rheumatoid disease. Exhaustive studies were performed throughout the years in an attempt to arrive at a diagnosis, but the results were consistently negative. Chronic brucellosis, palindromic rheumatism, periodic disease, and a collagen disorder other than rheumatoid arthritis were all considered. Perhaps the most striking feature in this case was the patient's apparent good state of health and freedom from all symptoms during the comparatively long periods of remission.

The value of the penicillin therapy was never established; at no time was a placebo injection given. The patient, however, felt strongly that the antibiotic was beneficial; hence it was given for the more severe and protracted febrile episodes. Since a leukocytosis was almost invariably present, the remote possibility existed that a penicillin-sensitive microörganism, primary or secondary, might be contributing to the fever. In retrospect, with the diagnosis of Whipple's disease established, it is most unlikely that the pencillin could have exerted any favorable effect. Secondary bacterial infection, except as a terminal event, is not a feature of this disease.

The development of persistent left-sided abdominal pain and a palpable mass made exploration mandatory. In the cases of Whipple's disease reviewed by Farnan, an abdominal mass was found in 22%, distention in 43%, and abdominal pain and tenderness in 37%. The preoperative diagnosis was retroperitonial neoplasm, most likely a lymphoma. In an attempt to relate the abdominal mass to the chronic, nondeforming polyarthritis, Whipple's disease was considered, but was erroneously discarded because of the absence of steatorrhea after more than 13 years of arthritis. At laparotomy, the pathologic findings in the small intestine and mesentery were entirely in keeping with the

diagnosis of intestinal lipodystrophy. The abnormal tissue was so indurated, however, that a detailed exploration of the gastrointestinal tract was carried out in a search for primary neoplasia. It was only after biopsy material from the nodes and mesentery was obtained that the fat content of the tissue could be appreciated.

As previously indicated in the report of the operative findings, dilated lacteals were found in the mesentery. Since publication of the paper by Hendrix et al.[8] there has been controversy in the literature about the significance of this finding. According to these authors, lacteal obstruction is not a feature of Whipple's disease since, as observed in their excellent review, patients who otherwise met their criteria for diagnosis had no evidence of lymphatic obstruction, while several who failed to meet these criteria did also show lymphatic obstruction, as evidenced by dilated lacteals and chylous ascites. Many authors have subsequently reported on patients who clearly had Whipple's disease and who also showed lacteal obstruction.[2, 9, 10] It can be stated, therefore, that lacteal obstruction, per se, does not rule out Whipple's disease, provided the definitive histopathologic features are present, as they are pathognomonic.

In his original paper, Whipple noted that most of the fat in the bowel wall and mesentery was extracellular.[1] Some of the fat is within macrophages, but most of the so-called foamy macrophages are nonsudanophilic.[1, 11] Black-Schaffer in 1949 demonstrated that the material within the macrophages in the intestine and mesenteric nodes is a glycoprotein, since it stains positively with the periodic-acid-Schiff stain.[12] This finding was confirmed by Upton in 1952.[13] The sudanophobic, or PAS-positive, macrophage is essential to the diagnosis. As expressed by Puite and Tesluk: "At present, the only safe criterion for diagnosis would appear to be the characteristic PAS-positive macrophage in the typical distribution, regardless of other findings."[14] Sieracki further observed that this PAS-positive material often appeared as cytoplasmic particles, with a configuration similar to sickled erythrocytes with sharply pointed ends.[11, 15] These particles have since been referred to as Sieracki bodies, and the cells which contain them as the sickle-form particle-containing (S.P.C.) cells.[11] The patient here described showed both the amorphous PAS-positive material and Sieracki bodies. With the histopathologic and histochemical criteria well established, it has become possible to confirm the diagnosis of Whipple's disease in a clinically suspect case without resorting to laparotomy. This may be accomplished either by peripheral lymph node biopsy[13, 14] or by means of the Shiner small intestine tube.[16]

Fever was present in 22% of the cases reported by Farnan. In none of these, however, was the pattern similar to that found in the case presented here, where the duration of intermittent fevers is more than 13 years. Puite and Tesluk reported fever in three of their four cases, and they also described "cycles of fever" in which maximal temperature would be reached by the fifth to seventh day, followed by a brief free interval.[14] They also found that shaking chills and drenching night sweats were often present in these cycles. Fever, when present, tended to be a feature of the terminal or near-terminal phase of the disease, in contrast to the situation in this case. In view of the fact that no other explanation for his fevers was ever found during the 12-year

period of careful observation, it seems reasonable to accept these fevers as a manifestation of Whipple's disease.

Since symptoms were present for 18 months before the patient was first seen in 1947, a total duration of disease of more than 13 years must be postulated. Plummer states that the average duration of the disease is 6.5 years in those manifesting arthritis, and 2.1 years for those with abdominal pain and diarrhea but no joint symptoms.[9] According to Farnan, the disease can last as long as 23½ years.[2] In Jarcho's case, arthritis antedated abdominal symptoms by 13 years, with death occurring two years after the onset of intestinal manifestations.[17]

Arthritis occurred in 61% of the reported cases, and appeared as the initial complaint in about half.[2, 9] When polyarthritis was present, it almost always antedated diarrhea and abdominal symptoms.[9] The findings in the joints are characteristically more suggestive of rheumatic fever than of rheumatoid arthritis, though in a few instances a clinical picture indistinguishable from rheumatoid arthritis is described.[14] In most of the reported cases, however, residual deformity was not observed, and involvement was almost always restricted to the peripheral joints. This was essentially the clinical course of the arthritis in the patient under discussion. The arthritis of Whipple's disease is felt to be a manifestation of a generalized polyserositis, involving not only the synovia but also the pleura, the pericardium, and, rarely, the endocardium. No other serosal involvement has been manifested in this case.

Asthenia, skin pigmentation, and hypotension occurred in more than half of the reported cases; hence the possible role of adrenal insufficiency as a factor in this disease has received considerable attention.[10, 14, 18] No acceptable evidence for Addison's disease has ever been presented, however, and the newer tests of adrenal cortical responsiveness have given uniformly negative results in Whipple's disease. Furthermore, as will be discussed below, many patients have experienced satisfactory remission after ACTH, even in certain instances where they had failed to respond to exogenous cortisone.[19] The case here presented showed no clinical or laboratory features suggestive of adrenal cortical insufficiency.

Steatorrhea and the malabsorption syndrome probably represent the most important manifestations of Whipple's disease. As has been indicated, however, these symptoms may not appear until relatively late in the course of the disease, particularly when arthritis has been the initial complaint. In the patient presented, constipation, not diarrhea, has been the pattern thus far. In spite of this, the findings at laparotomy of a markedly thickened intestinal wall and lymphatic blockage in the mesentery lead one to suspect that malabsorption is indeed present, and might well become clinically manifest in the near future. It was therefore felt to be of interest to evaluate small intestinal absorptive function at this stage of the disease.

The laboratory values suggest that a defect in intestinal absorption does exist, but they certainly fail to substantiate the presence of a generalized malabsorption syndrome. The fasting carotene level was low but was within normal limits, as was the glucose tolerance test. The results of the vitamin A tolerance test were of interest in that they showed an apparent delay in absorption, as indicated by the peak of the curve at the ninth hour (later than

the mean normal). There was no significant increase in the quantitative fecal fat excretion. The abnormal motor physiology of the small intestine demonstrated on the x-ray study was not surprising, in view of the previous laparotomy findings. Nevertheless, the radiographic abnormalities were what one might expect in a malabsorption syndrome, though the correlation is not necessarily good between the degree of x-ray change and the severity of the absorptive defects.

The I^{131}-labeled triolein test yielded values which are definitely abnormal by currently acceptable criteria, and indicate an impairment of fat absorption in this patient. There is not, as yet, universal agreement on the implications of the test, particularly when the values are borderline or only moderately depressed. The curve obtained here, however, is sufficiently abnormal so that there is little doubt of the interpretation. Further investigations might well prove that the absorption of triolein-I^{131} will be one of the most sensitive measures of intestinal absorptive function.

The fact that there is laboratory evidence for malabsorption in the absence of clinical manifestations is entirely in keeping with current concepts. It is increasingly appreciated that patients with isolated defects in absorption may continue in apparent good health for many years, without steatorrhea or gastrointestinal symptomatology of any sort, before signs of deficiency become evident. This was one of the factors that led to the decision to institute treatment with steroids in this patient.

There are several favorable reports in the literature on the effect of ACTH and cortisone in Whipple's disease. Jones et al. were the first to use steroids in this disease, and they achieved a complete remission in their patient with ACTH followed by oral cortisone. At the time of their publication the remission had lasted for 17 months, with maintenance therapy discontinued after two months.[10] Successful remission was observed in Lepore's case, where hydrocortisone proved to be considerably more effective than was cortisone.[7] One case of Puite and Tesluk, and two of Farnan's cases, had brief remissions on corticoid therapy which could not be sustained, and their patients died in spite of increased dosage of the drugs.[2, 14] Wang et al., reviewing the results of steroid treatment in Whipple's disease through 1956, cite eight treated cases, including their own, six of whom sustained a remission.[18] It is suggested by these authors that treatment instituted early in the course of the disease might result in the mobilization and perhaps the removal of the abnormal glycoprotein. It certainly would seem reasonable to assume that the considerable degree of inflammation and fibrosis seen in this disease would be partially inhibited by corticotherapy.

In the patient under discussion, the increase in appetite, weight, and well being after 6-methylprednisolone was started was not sufficiently marked to warrant the hazards of prolonged therapy. Of far greater significance, however, was the complete subsidence of arthritis, abdominal pain, and bloating, and the control of the fever. The two brief febrile episodes which did occur during the 90-day treatment period were self-limited and did not require an increase in the dosage of the drug for control. It is planned to continue steroids indefinitely, titrating the dosage against recurrence of fever.

The pathogenesis of Whipple's intestinal lipodystrophy is unknown, though the opinions of several recent authors may be summarized to form a reasonable working hypothesis. After the demonstration by Black-Schaffer of the abnormal glycoprotein in the intestinal mucosa and draining lymph nodes, the disease could no longer be considered to be simply a disorder of fat metabolism. When Upton, and later Puite and Tesluk, showed the glycoprotein to be present not only in mesenteric nodes but also in peripheral nodes, liver, spleen, and endocardium, the disseminated nature of the process became more fully appreciated.

Polyarthritis, polyserositis, and fever are perhaps explained by the development of a hypersensitivity state in response to the formation and systemic dissemination of the abnormal protein. Certainly these findings have come to be accepted as features of the allergic or hypersensitivity group of disorders. Though undoubtedly an oversimplification, intestinal malabsorption itself could be explained by lacteal obstruction mechanically produced by the glycoprotein in the intestinal mucosa and draining lympatics. The fat is largely extracellular, which is what one might expect if the normal channels for absorption were partially occluded. Secondarily, the accumulation of large amounts of fat could then further increase the mechanical blockage. The finding of a small number of "lipid-laden" macrophages, and the formation of granulomata in the lymph nodes, suggest a foreign-body type of reaction to the presence of the large amount of extracellular fat. The addisonian-like picture is not the result of a primary adrenal defect, but is more analogous to that seen in nontropical sprue, where specific malnutrition secondary to malabsorption may be the prime factor. The addisonian-like features in Whipple's disease are generally found in those cases where steatorrhea and malabsorption have been present for a long time, lending support to this hypothesis.

If, therefore, one presumes the formation of the abnormal glycoprotein to be the first pathologic event, then the major features of the disease—malabsorption, polyarthritis, and polyserositis, and the addisonian-like picture—may be brought together into a unified concept. Furthermore, such a hypothesis would explain why arthritis could antedate intestinal symptoms in approximately half of the reported cases. The arthritis, representing a protein hypersensitivity phenomenon, could develop as soon as a "sensitizing" amount of the abnormal protein had been formed or disseminated. Steatorrhea and malabsorption would be more dependent upon the absolute amount and perhaps the rate of formation of the protein, since in this situation it is responsible for the mechanical blockade of a large lymphatic drainage system. While there is as yet no explanation for the formation of the abnormal glycoprotein, it seems reasonable to assume that the underlying defect responsible for its formation rests in the connective tissue of the intestinal mucosa. If this be true, then Whipple's disease would be linked to that larger group of disorders, the diseases of connective tissue.

Summary

A case of Whipple's intestinal lipodystrophy is presented. This is the eighty-eighth case to be reported, and the seventieth that fulfills all of the pathologic criteria. The case is of particular interest in that recurrent fevers

and polyarthritis were the major clinical features for 13½ years. The diagnosis was established by laparotomy, performed after the development of abdominal pain and a tender abdominal mass. At no time have there been the clinical features of a malabsorption syndrome, though triolein-I^{131} studies indicated an impairment of fat absorption. The patient had a remission of all symptoms on adrenal steroid therapy, instituted in an attempt to control the recurrent fevers and, it was hoped, to arrest the progress of the disease. The salient clinical and pathologic features of Whipple's disease are discussed, particularly as they relate to this case. Newer technics of diagnosis and the principles of therapy are reviewed, and the current concept of pathogenesis is presented.

Addendum

In July, 1960, the patient was again hospitalized because of weakness and edema. He had not experienced any further joint pains, and only on rare occasions had his temperature risen to 100.5° F. There had been no diarrhea.

On admission, the significant findings were a hemoglobin of 7.6 gm., a serum albumin of 2.7 gm., and repeatedly positive stool guaiacs. A gastrointestinal series revealed a normal stomach and duodenum with no evidence of ulceration. The jejunum and ileum showed thickening of the mucosal folds with flocculation and segmentation of the barium. The bleeding was presumed to be due to the underlying disease, and was treated by blood replacement. The

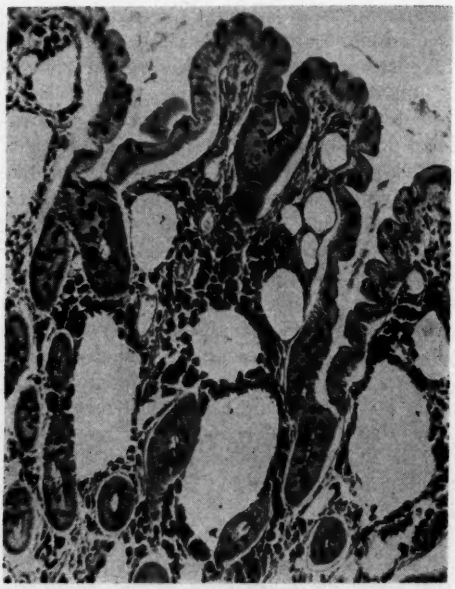

Fig. 6. Section of jejunal mucosa, PAS stain. The villi are thickened and reduced in height. Dark staining clumps in the lamina propria represent aggregates of PAS-positive material, most of which is intracellular. Note multiple, large fat spaces throughout the lamina propria.

steroid dosage was increased to 50 mg. of prednisone daily, and a partial remission was again achieved with improvement in appetite and strength, and cessation of bleeding. During this admission, a jejunal biopsy was performed by intestinal intubation. Characteristic PAS-positive material was demonstrated in the lamina propria, diagnostic of Whipple's disease (Figure 6).

ACKNOWLEDGMENT

The author wishes to express his gratitude to Dr. C. H. Traeger for permission to report this case.

SUMMARIO IN INTERLINGUA

In 1907, Whipple describeva un morbo in un masculo de 36 annos de etate, characterisate per steatorrhea, debilitate, perdita de peso, anemia, polyarthritis, e tusse. Depost ille tempore, 69 casos con provas pathologic del mesme entitate ha essite reportate. Le morbo es frequentemente considerate in le diagnose differential de syndromes de malabsorption intestinal.

Le septantesime caso de morbo de Whipple es hic presentate. Illo es de interesse inusual, viste que febres recurrente e polyarthritis esseva le sol aspectos clinic durante plus que 13 annos. Le diagnose esseva establite per laparotomia effectuate a causa del disveloppamento de un palpabile massa abdominal. Al operation, le intestino tenue se monstrava spissificate e del consistentia de cauchu. Le mesenterio esseva reimplaciate in grande mesura per indurate tissu grasse e allargate nodos mesenteric plenate de grassia. Le examine histologic revelava characteristic macrophagos spumose que se tincturava positivemente con le tinctura de acido periodic de Schiff. (Isto indica le presentia de glycoproteina in le macrophagos e representa un corroboration histologic del diagnose.)

Malabsorption intestinal, nunquam clinicamente manifeste in iste patiente, esseva demonstrate per studios con trioleina a I^{131}. Le patiente esseva tractate con un therapia de steroides adrenal in le spero que assi le progresso del morbo poterea esser arrestate. De facto, le therapia causava un subsidentia del febre, e le dolores articular dispareva completemente.

Le pathogenese de morbo de Whipple non es cognoscite, sed il pare probabile que le characteristicas clinic es causate per le formation del glycoproteina anormal. Iste material poterea producer malabsorption per un blocage mechanic de canales lymphatic intestinal e mesenteric (lacteales). Le symptomas systemic de febre, arthritis, e polyserositis representa probabilemente un hypersensibilitate pro le proteina anormal.

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POLYCYTHEMIA AND HYDRONEPHROSIS *

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Twenty-five years ago an association between polycythemia and renal carcinoma was suspected and reported in the literature.[1] Two years ago a case was described of polycythemia associated with unilateral hydronephrosis where the polycythemia was corrected following removal of the diseased kidney.[2] Subsequently, four additional cases have been reported concerning the associa-

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tion of hydronephrosis with polycythemia.[3-5] It has been theorized that an erythropoietic stimulus arises from the diseased kidney, inasmuch as the polycythemia is corrected upon its removal.[6]

The following case is another instance of the association of marked polycythemia and unilateral hydronephrosis, with remission of the polycythemia following nephrectomy. Efforts were made to isolate "erythropoietin" from the renal vein of the diseased organ prior to surgical removal.

Case Report

A 62-year-old white male was first admitted to the hospital on December 6, 1958, because of weakness of the right arm and leg of seven days' duration. Two and one-half years prior to admission he had sustained a progressive paralysis of the left arm and leg. He recovered sufficiently to resume work as a cook, and had done fairly well until three weeks prior to admission, when he developed mental confusion and weakness of the right extremities. Seven days prior to admission there was definite progression of the right hemiparesis, and the patient became unable to stand alone. He had had orthopnea for the last two years; otherwise his past history and family history were noncontributory.

Physical examination revealed a well nourished white man who was slightly confused. Blood pressure, 140/90 mm. Hg; pulse, 86/min.; temperature, 98° F. There was an erythematous macular rash over the skin of the face, neck, and arms. The chest examination revealed evidence of pulmonary emphysema. The spleen was palpable 6 cm. below the left costal margin. Neurologic examination showed right homonymous hemianopsia and spastic hemiparesis of the right arm and leg.

Laboratory Data (Table 1): Hemoglobin, 23.5 gm.%; hematocrit, 71%; white blood cell count, 10,900/cu. mm., with a normal differential count; platelet count, 230,000/cu. mm. Urinalysis showed 10 mg.% albumin and no glucose, with numerous white blood cells and 10 to 15 erythrocytes per high power field. Blood urea nitrogen, 12 mg.%; liver function tests, normal. A chest x-ray showed prominent vascular markings in both lung fields. Skull x-ray was negative. Intravenous pyelograms revealed a large left kidney but no excretory function. The right excretory system appeared to be normal. Retrograde pyelograms showed a dilated and displaced left renal pelvis.

The arterial oxygen saturation, breathing room air, was 89%, and 100% (plus 0.96 vol.%) after breathing 100% oxygen for eight minutes. The total blood volume determination by Cr^{52}-tagged erythrocytes was 5,113 ml., with a calculated normal of 5,470 ml. The red cell mass was 3,027 ml., with a calculated normal of 2,115 ml. Pulmonary function studies showed an increase in both total lung capacity and residual volume compatible with mild to moderate pulmonary emphysema (Table 1).

On December 30, 1958, a cardiac catheter was introduced into the right median cubital vein and advanced to the level of the left renal vein, where 400 ml. of blood were removed and a biologic assay of erythropoietin activity was determined.* An arterial dye dilution curve was obtained at the same time.

Hospital Course: In preparation of the patient for surgery, 1,700 ml. of blood were removed by venesection over an 18-day interval. On January 15, 1959, a left nephrectomy was done. The surgical specimen consisted of a multilocular cystic structure having a total weight of 107 gm. Microscopic examination revealed only remnants of the kidney tubules and glomeruli. The pathologic diagnosis was hydronephrosis of undetermined cause. In August, 1959, nine months following surgery, the spleen was no longer palpable. Hemoglobin, 15.7 gm.%; hematocrit, 48%; white

* Courtesy of John McCarty, M.D., and Neal Gallagher, M.D., Veterans Administration Hospital, St. Louis, Missouri.

TABLE 1

Laboratory Studies Preoperatively and 10 Months Postoperatively

Date	Body Weight (lbs.)	Hemoglobin (gm.%)	Hematocrit (%)	Red Blood Cells (M/cu. mm.)	White Blood Cells (cu. mm.)	Platelets (cu. mm.)
12-6-58 Preop.	155	23.5	71		10,950	230,000
9-24-59 Postop. 10 months	149	14.6	44	4.91	8,050	432,000

Date	Blood Volumes (ml./Kg.)			Arterial Oxygen Saturation (%)		Pulmonary Function (ml.)		RV* / TLC
	Total Blood Volume	Plasma Volume	Red Cell Volume	Room Air	After Oxygen	Residual Volume	Total Lung Capacity	
12-6-58 Preop.	72.4	29.5	49.9	89	100%+ 0.96 vol. %	3,077	5,877	51%
9-24-59 Postop. 10 months	55	31	24	92.7	100%+ 0.17 vol. %	3,319	6,118	54%

* $\frac{RV}{TLC} = \frac{\text{Residual volume}}{\text{Total lung capacity}} = 20\text{–}30\%$.

Normal values:

Total blood volume = 61–76 ml./Kg.
Plasma volume = 33–41 ml./Kg.
Red cell volume = 26–30 ml./Kg.

blood cell count, 14,108/cu. mm. One month later the hemoglobin was 14.6 gm.%; hematocrit, 44%; white blood cell count, 8,050/cu. mm.; erythrocyte count, 4,910,000 /cu. mm. (Table 1).

DISCUSSION

To our knowledge, this is the sixth case of polycythemia associated with hydronephrosis that has been reported in the American literature (Table 2). The dramatic hematologic improvement in this patient following nephrectomy is evident from Table 1. However, a longer follow-up time will be required to determine whether remission is complete.*

The mechanism of erythrocytosis occurring with certain types of renal lesions, particularly renal carcinoma, is unknown. It has been postulated that "erythropoietin" is produced by the diseased kidney or within the tumor.[6] The studies performed on blood obtained from the left renal vein of this patient prior to surgery showed no evidence of erythropoietic-stimulating properties. It is noteworthy that our patient did have an arterial oxygen desaturation of 89%; this, we feel, is due to pulmonary insufficiency secondary to pulmonary emphysema and pulmonary fibrosis, demonstrated by pulmonary function tests and confirmed by persistent desaturation of arterial blood one year after the disappearance of the polycythemia. It is unusual for polycythemia vera to have

* In February, 1960 (15 months postoperatively), the hemoglobin was 15.0 gm.%; hematocrit, 46%; white blood cell count, 14,800/cu. mm.; erythrocyte count, 5,500,000/cu. mm.

TABLE 2

	Cooper and Tuttle[3]	Gardner and Freymann[3]	Lawrence and Donald[5]	Lawrence and Donald[5]	Castleman and Kibbee[4]	Martt, Sayman and Neal
Age (yrs.)	55	65	36	37	62	62
Hb. (gm.%)	19	21.4	17	21.6	21.8	23.7
Hct. (%)	68	68			67	71
RBC (1×10^{-5})	9.85 M	6.88 M	6.00 M	8.86 M		
WBC (per cu. mm.)	11,300	11,050	16,000	5,920	10,800	10,900
Platelets (per cu. mm.)	360,000	"Normal"	490,000		238,000	230,000
Bone marrow	Normal	Erythroplasia				Normal
Palpable spleen			+ (?)			+
Arterial O_2 saturation		"Normal"		95.5%		89%
X-ray	Nonfunctioning left kidney	Hydronephrosis, right kidney		Abdominal mass, R.U.Q.	Abdominal mass, R.U.Q.	Hydronephrosis, left
Nephrectomy	+	+	+	+	Autopsy	+
Blood volume (ml.)*	T.B.V. 7,750 (Normal = 5,800) Pl. V. 2,840 (Normal = 3,020)	T.B.V. 5,120 Pl. V. 2,135 R.C. 2,995				T.B.V. 5,113 (Normal = 5,147) R.C. 3,027 (Normal = 2,115)
Pathology findings	Left hydronephrosis due to ureteropelvic obstruction with renal calculi	Right cystic, hydronephrotic kidney	Fibromyxoma and hydronephrosis	Left hydronephrosis due to ureteral band	Right hydronephrosis due to ureteral stricture	Left hydronephrosis, undetermined cause

* T.B.V. = total blood volume.
R.C. = red cell mass.
Pl. V. = plasma volume.

this low an arterial saturation.[7] A venous-arterial shunt in the lung or heart as a cause of polycythemia was excluded by arterial dye dilution curves. It would be untenable to conclude that the polycythemia resulted from pulmonary insufficiency, since the secondary polycythemia due to primary lung disease rarely, if ever, gives rise to a hematocrit of the magnitude seen in this patient.[7] As with other reports of this entity, we have no explanation of the mechanism of the polycythemia.* Gardner and Freymann[3] estimated that approximately 1% of patients with the diagnosis of polycythemia vera will be discovered to have renal cell carcinoma, and approximately 1% of patients with renal carcinoma will have polycythemia. Numerous cases of hypernephroma with polycythemia have now been reported.[4, 8-12] Certainly, there is sufficient evidence at hand to demand a careful urologic evaluation in all patients with unexplained polycythemia.

Summary

A case is reported of polycythemia associated with unilateral hydronephrosis. This is the sixth case reported in the medical literature.

The polycythemia was corrected by phlebotomies prior to left nephrectomy, and has not recurred 11 months following surgery.

Studies for erythropoietin in blood obtained from the left renal vein were negative.

The mechanism of the polycythemia complicating certain renal diseases is still unknown.

Summario in Interlingua

Es reportate un caso de polycythemia associate con hydronephrosis unilateral. Isto es le sexte caso del mentionate combination que se trova reportate in le litteratura medical.

Un masculo de 62 annos de etate se presentava con un hemoglobina de 23,5 g pro 100 ml, un hematocrite de 71 pro cento, un leve leucocytosis, e splenomegalia. Hydronephrosis del ren sinistre esseva discoperite post studios radiographic del vias genito-urinari, e le ren sinistre esseva excidite subsequentemente. Ante iste operation, un catheter cardiac esseva avantiate via le vena cave inferior usque al orificio del vena renal sinistre ubi 400 ml de sanguine total esseva prendite via le catheter pro objectivos de essayages pro activitate de erythropoietina. Iste studios esseva negative. Le polycythemia esseva corrigite ante le chirurgia per medio de phlebotomias. Dece-tres menses post le nephrectomia le numeration sanguinee monstrava le sequente valores: Hemoglobina 15,0 g pro 100 ml; hematocrite 46 pro cento; leucocytos 14.800; erythrocytos. Le splen habeva cessate esser palpabile.

Le mechanismo per le qual polycythemia occurre como complication de certe morbos renal—particularmente carcinoma renal—non es cognoscite. Le theoria que le interessate ren (o tumor) produce erythropoietina o un factor erythrocyto-stimulatori non esseva supportate per studios del sanguine de vena renal in le caso del patiente hic reportate.

Le disparition de polycythemia post le ablation del afficite ren es reportate etiam per alteros, particularmente in casos de carcinoma renal. Il existe nunc datos in quantitates sufficiente pro justificar le recommendation de un meticulose evalutation urologic in patientes con polycythemia de etiologia obscur.

* Since submission of this paper for publication, erythropoietin has been isolated from a cyst wall and from fluid within the cyst in a patient with polycythemia and a large unilocular cyst of the kidney, by Nixon et al. (Arch. Intern. Med. **106**: 797, 1960).

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OPISTHORCHIASIS WITH PULMONARY INVOLVEMENT*

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The first clinical description of opisthorchiasis in Thailand was made by Prommas in 1927.[1] Pradatsundarasar in 1950[2] recorded 31 instances of liver fluke infestation due to *Opisthorchis viverrini* observed between 1945 and 1949 in the Department of Pathology of the Siriraj Hospital. In 1952 and 1953 Sadun and Vajrasthira[3, 4, 5] reported the prevalence of opisthorchiasis in the northeastern part of Thailand, and estimated that not less than 1,500,000 among the

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Thai population of 18,000,000 in 1952 harbored the parasite. Viranuvatti and Mettiyawongse in 1953 [6] reported the concurrence of opisthorchiasis with carcinoma of the liver in two patients. In 1955 Viranuvatti et al.[7] reported a case of retention cyst of the liver caused by opisthorchiasis associated with carcinoma. A case of opisthorchiasis with upward spread to the lung is presented here.

Case Report

A 37-year-old male Thai farmer, residing in the northeastern part of Thailand, was admitted to the medical service of Siriraj Hospital because of jaundice of three months' duration. Four months prior to admission, symptoms had begun with fever, frequent chilliness, and marked prostration. The urine was dark in color. One month later the patient developed jaundice, which gradually increased in intensity. He also began to cough up small amounts of whitish mucoid sputum, and had pain

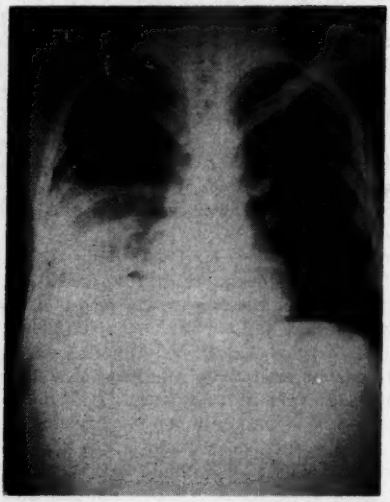

Fig. 1. Posteroanterior film of the chest, showing the pulmonary lesion in the right lower lobe.

in the right shoulder region on violent coughing. One month before admission his cough became more frequent, and was productive of greenish, tenacious sputum. About 100 to 200 ml. of sputum were expectorated; it had a bitter taste but not a foul smell. Coughing was worse when the patient was recumbent. There was also pain in the right hypochondrium, referred to the right shoulder. An abdominal mass was noticed by the patient himself. This occupied the right upper abdomen and was slightly tender. He became progressively weaker, anemic, and constipated.

There was a history of malaria and taeniasis 20 years before. Personal history was noncontributory. When the patient was very young his father died of emaciation, cough, and jaundice. Other relatives were still living.

Physical examination on admission revealed a thin man with dark complexion and obvious jaundice. Temperature, 38.5° C.; pulse, 117; respiration, 26; blood pressure, 124/74 mm. Hg. The upper abdomen was bulging, but there were no superficial dilated veins. The liver was palpable three fingerbreadths below the right

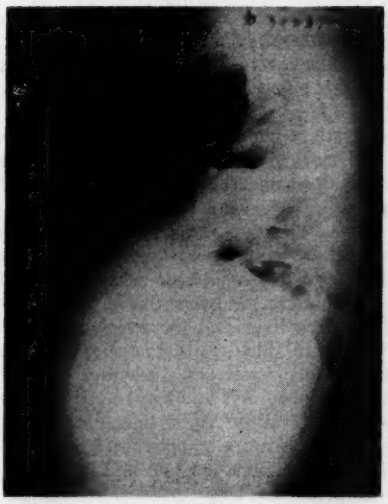

FIG. 2. Right lateral film, same case.

costal margin; the edge was not sharp, and there was no tenderness. There was diminished movement of the right lower chest, with dullness on percussion over the right interscapular and infrascapular regions. Increased vocal resonance and fine crepitations were detected over the area.

Laboratory Findings: The white blood cell count was 15,100/cu. mm. Differential count: polymorphonuclears, 72%; lymphocytes, 14%; eosinophils, 4%. Hemoglobin, 10.5 gm.%, red blood cell count, 3,600,000/cu. mm. The urine was positive for bile but was otherwise negative. Opisthorchis ova were present in the feces. The sputum was green, and showed gram-positive cocci and gram-negative bacilli. A sputum culture was positive for *Alcaligenes faecalis*. The test for bile in the

FIG. 3. X-ray film of the upper abdomen, showing finger-like appearance of the dilated biliary tract and a connecting tract between the liver and the lung (after introduction of Pyelosil solution into the liver).

sputum was positive. There were no parasitic ova in the sputum. The blood creatinine level was 1.9 mg./100 ml.; nonprotein nitrogen, 26.1 mg./100 ml. Cephalin flocculation test, 2-plus; iodine test, 4-plus; alkaline phosphatase, 23 Bodansky units. A roentgenogram of the chest showed a large area of consolidation in the right lower lung field.

After admission the patient had a high, intermittent fever (37.4° to 39.7° C.), with shallow dyspnea and marked prostration. On the fourth day of admission an aspiration of the liver was done under fluoroscopy. About 20 ml. of thin, greenish-yellow fluid were obtained. There were no parasites or ova in the aspirated fluid. Through the aspiration needle, 40 ml. of 50% Pyelosil solution were introduced. Under fluoroscopy the Pyelosil solution was observed to occupy the dilated biliary canals in the liver, and some of the radiopaque substance was found in the lower part of the chest (above the diaphragm). From this it was concluded that there was a definite connection between the liver and the lesion in the lung. Despite intensive treatment, including Terramycin, dihydrostreptomycin, chloroquine, and erythromycin, the patient became progressively worse and died after three weeks in the hospital.

Autopsy Report (Department of Pathology): Advanced opisthorchiasis (*Opisthorchis viverrini*), parasitic cyst of right lung, presumably in connection with the right lobe of the liver (microscopically, opisthorchis ova were seen to be embedded in several foci of the lung parenchyma); acute and chronic pyelonephritis, bilateral; nephrolithiasis, left; hydronephrosis, left.

Discussion

The diagnosis of opisthorchiasis in this case was established by the repeated finding of the ova in the feces. The pulmonary lesion in the right lower lung field, with greenish sputum which showed a positive bile test, suggested a connection with the biliary tract. *A. faecalis* found in the sputum was interpreted as a secondary invader. The introduction of radiopaque substance into the liver showed finger-like dilatations of the biliary tract. This is typical of advanced cases of opisthorchiasis. The radiopaque substance was also found in the lower lung field, suggesting the presence of a connection between the liver and the lesion in the lung. This was confirmed at autopsy. A thorough search of the available literature fails to disclose any previously reported case of intrathoracic opisthorchiasis diagnosed ante-mortem.

Summary

A case is presented of opisthorchiasis with pulmonary involvement, proved by the introduction of radiopaque substance into the liver and confirmed at autopsy. This is the first case of its kind to be reported.

Acknowledgment

We wish to express our sincere gratitude to Dr. Prasert Kangsdal for his advice in the preparation of this paper, and to Dr. Pradit Tansurat, who kindly let us have the results of the pathologic study.

Summario in Interlingua

Es reportate un caso de opisthorchiasis con affection pulmonar. Le patiente, un thai mascule de 37 annos de etate, esseva hospitalisate con le constatation de jalnessa de un duration de tres menses, un hepate allargate, dolores thoracic al latere dextere,

e un frequente tusse con production de sputo de color verdastre. Le test pro bile in le sputo esseva positive. Un roentgenogramma del thorace monstrava un grande area de consolidation in le campo pulmonar dextero-inferior. Le diagnose de opisthorchiasis esseva establite per le constatation del presentia de oves de opisthorchis in le feces. Le introduction de un substantia radio-opaque in le hepate monstrava in le fluoroscopo un dilatation dactyliforme del vias biliari. Isto es un constatation typic in casos avantiate de opisthorchiasis. Un parte del substantia radio-opaque esseva etiam trovate in le parte dextero-inferior del pulmon. Isto pareva indicar que il existeva un connexion inter le hepate e le lesion in le pulmon dextero-inferior. Le patiente se deteriorava progressivemente in despecto de un intense therapia. Ille moriva post un sojorno de tres septimanas al hospital. Le necropsia monstrava opisthorchiasis avantiate (per *Opisthorchis viverrini*) con cystes parasitic in le pulmon dextero-inferior. Ovos de opisthorchis esseva etiam constatate microscopicamente in plure focos del parenchyma pulmonar.

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MARKEDLY ELEVATED BLOOD AMMONIA IN A PATIENT WITH CONSTRICTIVE PERICARDITIS *

By Albert A. Fisk, M.D., *Elyria, Ohio*

Elevated blood ammonia levels have been found to be an important aspect of primary liver diseases, both acute and chronic, and the recognition of coma and precoma states due to ammonium ion intoxication has become an important part of the clinical management of patients with such liver diseases. However, elevations of the blood ammonia and secondary neurologic symptoms from such elevations have not commonly been found in patients with congestive heart failure. The following case report concerns a 51-year-old truck driver with chronic constrictive pericarditis who had markedly elevated blood ammonia

* Received for publication March 9, 1960.
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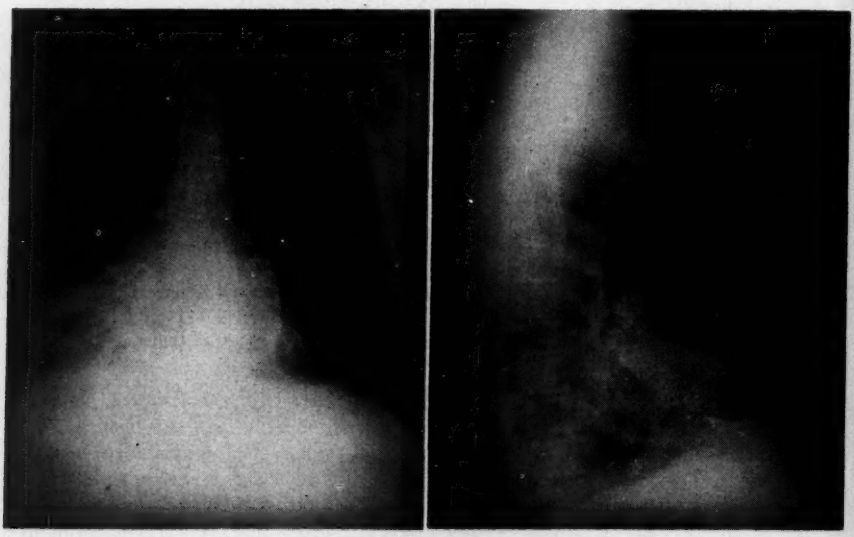
levels with secondary neurologic signs and symptoms. The elevated blood ammonia responded poorly to the usual medical management of such a problem, but following surgery the blood ammonia returned to relatively normal values.

Case Report

A 51-year-old male truck driver was admitted to the hospital as an emergency because of marked dyspnea and swelling of the abdomen associated with upper abdominal pain. The patient had complained of progressive dyspnea, weakness, and abdominal discomfort over the last three months, but had been able to work full time as a truck driver until one month prior to his admission to the hospital. On closer questioning the patient admitted he had not felt well during the preceding four or five



A B

Fig. 1. Posteroanterior (A) and lateral (B) chest x-rays taken in 1954, showing extensive calcification of the pericardium.

years, and had had periods of intermittent abdominal discomfort and abdominal swelling. Past history was negative except for an episode of hemoptysis in 1954, ascribed to a pneumonia. At this time the patient had had an infiltration in the right mid-lung field, but complete diagnostic studies were not carried out at that time as recommended. There was no past history of rheumatic fever or tuberculosis. The patient had a moderate alcohol intake, but had never been a heavy drinker, and usually ate well.

Physical examination on admission to the hospital revealed an extremely weak, pale, sweaty patient who was markedly dyspneic. The patient preferred to sit up, leaning forward in bed. The neck veins were markedly protuberant in the sitting position, and a mild scleral icterus was noted. Blood pressure was 95/80 mm. Hg; pulse, 130/min. and regular. Examination of the lungs revealed scattered moist râles over both bases posteriorly, and dullness to percussion at the right base up to the tip of

the scapula. The heart sounds were of poor quality and distant, but no murmur or gallop rhythm could be detected. The heart impulse could not be palpated, and the size was indeterminate by percussion. The abdomen was markedly protuberant, with obvious ascites and a huge, tender liver filling the entire upper abdomen. The spleen was not palpable. Examination of the extremities revealed a 2-plus pitting edema.

Chest x-ray on admission showed a normal-sized heart with calcification of the pericardium. The lung fields showed a pleural effusion at the right base, and engorged hilar markings. Review of a chest x-ray taken in 1954 (Figure 1) also revealed the calcified pericardium. Fluoroscopy of the chest showed no apparent pulsations of the heart. An electrocardiogram on admission showed low voltage in all leads, flat T waves in the left lateral chest leads, and inverted P waves in most leads. Venous pressure in the right antecubital fossa was 230 mm. of saline, and the Decholin circulation time, arm-to-tongue, was 20 seconds. A paradoxic pulse of 15 mm. was obtained. The white blood cell count on admission was 16,500/cu. mm., with 95% polymorphonuclear cells, and the hemoglobin was 13.8 gm.%. The blood ammonia, using the Conway procedure, was 343 μg.%. The serum sodium, potassium, chloride, CO_2, and nonprotein nitrogen were all within normal limits. The thymol turbidity was 2.5 units; serum albumin, 3.2 gm.%; serum globulin, 2.5 gm.%; total serum bilirubin, 2.1 mg.%; cephalin flocculation, negative. The prothrombin time was 18 seconds, with a control of 12 seconds. The second strength purified protein derivative was positive, but numerous sputum studies for acid-fast bacilli were negative after six weeks of culture. A diagnosis of chronic constrictive pericarditis was made, and during the next month a vigorous program was undertaken to attempt to improve the patient before surgery.

The patient was placed on a low salt, low protein diet, was digitalized, and was given mercurial diuretics and chlorothiazide. Despite attempts to achieve some semblance of cardiac compensation, the edema fluid increased and the patient remained in a very precarious clinical condition. The pulse and respirations remained rapid, and he complained bitterly of upper abdominal pain from the markedly distended, tender liver. The blood ammonia level remained highly elevated (Figure 2), and after two weeks of treatment the serum sodium was 117 mEq./L.; serum chloride, 78 mEq./L.; serum potassium, 4.8 mEq./L.; serum CO_2, 32 mEq./L.; nonprotein nitrogen, 35 mg.%. On the sixteenth hospital day the blood ammonia level (Figure 2) rose to over 700 μg.%, and the patient was noted to have a flapping tremor of his hands and to be very somnolent. He was started on neomycin, 1 gm./day orally, in an attempt to reduce the absorption of ammonia from the intestinal tract. When this maneuver failed to reduce the blood ammonia level, and it had risen to almost 800 μg.%, he was started on arginine monohydrochloride, 25 gm./day intravenously. He was also given dexamethasone to suppress aldosterone production by the adrenal gland. Although these methods resulted in some clinical improvement, and a drop in blood ammonia level, the patient remained in refractory congestive heart failure and appeared to be desperately ill. He had become massively edematous and ate poorly. He required meperidine for alleviation of his abdominal pain. Despite the failure of the medical regimen to improve his clinical condition, it was felt that surgical relief of the constriction was necessary if he were to survive much longer. He was therefore given streptomycin and isoniazid to control any possible tuberculous infection, and intravenous infusions of serum albumin preoperatively. Administration of intravenous hypertonic saline in small amounts improved the serum sodium, and with an increase in the amount of oral neomycin and intravenous arginine given, the blood ammonia level was reduced so that neurologic symptoms were no longer present.

After one month of vigorous but rather ineffective medical treatment, the patient was taken to surgery. He tolerated the surgical procedure surprisingly well, the

FIGURE 2

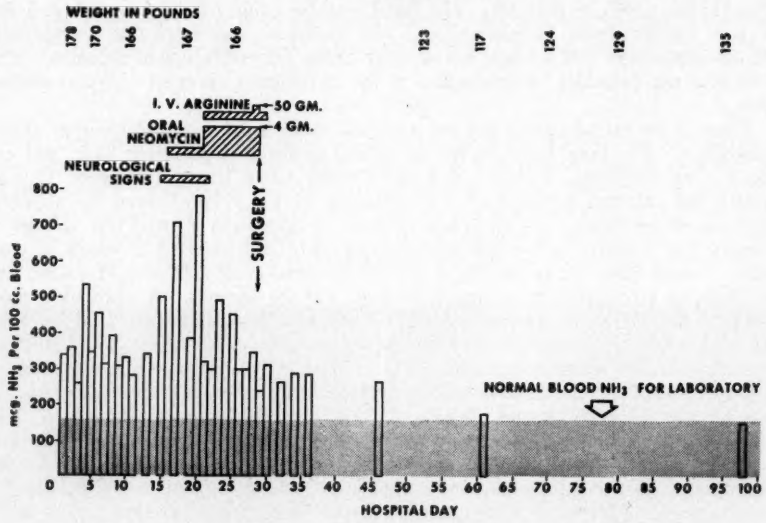


FIG. 2. Markedly elevated blood ammonia levels returned to normal after surgical relief of a constrictive pericarditis.

only cardiac problem being a few short-lived runs of ventricular tachycardia during the induction of anesthesia. The entire pericardium was found to be calcified, being up to a quarter-inch in thickness in some places, and inseparable from the myocardium at several spots. By careful dissection the pericardium was removed from the left and right ventricles, and the calcifications extensively involving the right auricle and the inferior vena cava were removed. Calcified pericardium around the pulmonary veins posteriorly was removed, but because of the critical condition of the patient an extensive dissection in this region was not possible. He was returned to the recovery room in satisfactory condition, but he had a prolonged and difficult postoperative course. However, he had a gradual, spontaneous diuresis, losing over 40 pounds of edema fluid. His serum albumin rose to 3.5 gm.%, his icterus disappeared, and his venous pressure dropped to 144 mm. of saline. The patient's blood volume, which had been 8,400 ml. prior to surgery, dropped to 6,800 ml. two days postoperatively, and to a normal level of 5,600 ml. three days postoperatively. The liver receded in size, the patient's edema disappeared, and he no longer presented a problem of refractory cardiac failure. He did develop a chronic pneumonitis and tracheitis, which responded slowly to various antibiotics. He became discouraged and was a serious nutritional problem, but after several weeks of vigorous nursing care and physiotherapy he gradually gained a few pounds and some degree of strength, and was able to be up and about his room. Two months postoperatively the patient was discharged. Before discharge a liver biopsy (Figure 3) was done, which showed only chronic passive congestion and cloudy swelling. Bromsulfalein test at the time of the biopsy showed 4% retention of dye in 45 minutes. On the day of discharge the blood ammonia had fallen to 150 μg.% (Figure 2), which is just slightly above normal for our laboratory. The patient's course since discharge has been one of gradual improvement. The chronic pneumonitis has slowly cleared, and his breath-

ing is now satisfactory. The liver remains enlarged (two fingerbreadths below the costal margin).

Discussion

This case represents far advanced constrictive pericarditis, with dyspnea, ascites, enlarged liver, and hypoalbuminemia. It has long been recognized that disturbed hepatic function plays an important part in the clinical picture of constrictive pericarditis. Lowered serum albumin levels have been a consistent finding in patients with constrictive pericarditis, and much of the edema and ascites has seemed to be on this basis. In 1941 Stadler and Stinger[1] reported a case of Pick's syndrome, and showed that the hypoproteinemia was the result of failure of the liver to synthesize serum albumin, rather than of a nutritional inadequacy of protein or an excessive renal loss. Other liver function studies were within normal limits, and histologically the liver showed a cardiac cirrhosis without evidence of bile stasis. Evans and Jackson[2] in 1952 reported a series of liver biopsies done on patients with constrictive pericarditis. The only abnormality found was a central fibrosis or a central hyperemia, and they felt that cardiac cirrhosis was a bad prognostic sign in constrictive pericarditis. There have been a few studies of blood ammonia levels in patients with congestive heart failure. Calkins and Delp[3] in 1956 reported three of 26 patients with congestive heart failure who had elevated blood ammonia levels. All three showed only slight elevations of the blood ammonia level, the highest being 231 μg.% (in a patient who also was a cirrhotic). The other two patients had lower levels; of these two, one had subacute bacterial endocarditis, with jaundice. Bessman and Evans[4] in 1955 reported blood ammonia levels determined by the Seligson method in nine patients with congestive heart failure. In these nine the elevations found were not striking, and were probably of no clinical significance. The present patient is of interest because the blood

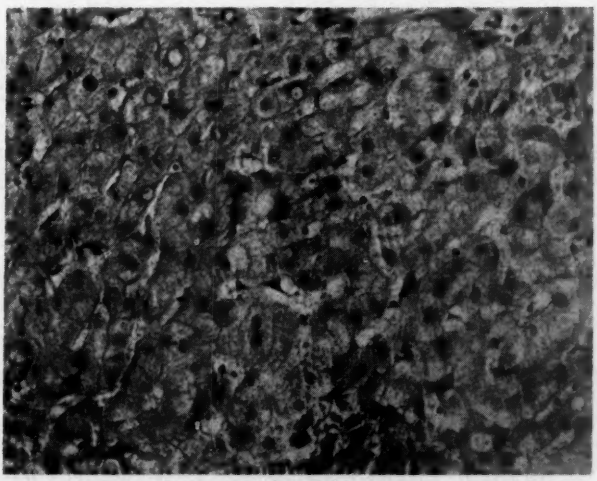


Fig. 3. Liver biopsy (× 600). Chronic passive hyperemia and cloudy swelling are present, without fibrosis or inflammatory reaction.

ammonia level found corresponds to that which may be found in patients who have decompensated cirrhosis of the liver, with coma, or acute, fulminating hepatitis. However, as is evident from the liver function studies, and from the liver biopsy (Figure 3), this patient did not have cirrhosis or hepatitis. We must therefore assume that the markedly elevated blood ammonia level found in this patient with constrictive pericarditis is analogous to a portal bypass of the liver, due to the constriction in the region of the inferior vena cava. One would assume that collateral venous channels which bypassed the portal system were well developed, and that the liver was therefore not able to metabolize the ammonia absorbed from the intestinal tract. When the constriction was relieved, the liver, although the site of some central lobular fibrosis, was capable of handling the ammonia load presented from the intestinal tract. It would be interesting to know whether other patients with constrictive pericarditis have elevated blood ammonia levels, and also whether patients with tricuspid stenosis do not occasionally present the same problem.

Summary

A markedly elevated blood ammonia level in a patient with chronic constrictive pericarditis is reported. After surgery, the blood ammonia returned to normal. Since no primary liver disease was found, it is presumed that a portal bypass resulted from the constriction in the region of the inferior vena cava.

Summario in Interlingua

Un masculo, chauffeur de camion, de 51 annos de etate esseva admittite al hospital con avantiatissime pericarditis constrictive, manifeste in dyspnea, ascites, hepatomegalia, e hypoalbuminemia. Al tempore de su hospitalisation, le ammoniaco sanguinee del patiente amontava—secundo le methodo de Conway—a 343 μg per 100 ml. Le studios routinari del function hepatic produceva valores intra le limites normal. In despecto de un adequate regime medical, consistente de prescriptiones dietari, de digitalisation, del uso de diureticos, e de allectamento, le patiente persisteva in un precari condition clinic, con marcate grados de dyspnea e debilitate como le symptomas le plus eminente. Le nivello sanguinee de ammoniaco esseva determinate diurnemente e remaneva in le region de 300 a 400 μg per 100 ml, sed le septime die del hospitalization illo montava a plus que 700 μg per 100 ml. A iste tempore il esseva notate que le patiente habeva un tremor battente in le manos e que ille esseva multo somnolente. Le tractamento con neomycina oral e arginina intravenose resultava in un melioration del nivellos sanguinee de ammoniaco e alleviava le symptomas neurologic. Post un mense de satis inefficace manipulationes medical le patiente esseva subjicite a un intervention chirurgic. Un extense pericardiectomia esseva executate. Postea le patiente experientiava un diurese spontanee de approximativemente 40 libras de liquido edematic, e le nivello sanguinee de ammoniaco retornava a valores normal.

Ante le dishospitalisation, un biopsia de hepate esseva effectuate. Illo revelava marcate grados de tumescentia nubilose sed nulle signo de fibrosis centro-lobular o de cirrhosis portal. Le marcatemente elevate nivellos sanguinee de ammoniaco trovate in iste patiente esseva presumitemente causate per chronic congestion passive del hepate e del integre systema portal, con le resultato de un circuition portal e le disfallimento del hepate in su function de distoxificar le iones de ammoniaco absorbite ab le intestino.

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PROLONGED FUNCTIONAL DEPRESSION OF ANTIDIURETIC MECHANISMS IN PSYCHOGENIC POLYDIPSIA SIMULATING PRIMARY DIABETES INSIPIDUS*

By Richard Wedeen, M.D., *New York, N. Y.*

The differential diagnosis of polyuria and polydipsia is a common problem. Increased renal water loss may occur with: (1) diabetes mellitus, (2) chronic nephritis, (3) severe thyrotoxicosis, (4) kaliopenic nephropathy, (5) hypercalcemia, (6) diabetes insipidus, both primary and nephrogenic, and (7) psychogenic polydipsia. The first five of this group can be differentiated by specific laboratory and clinical studies. There remains, however, the frequently encountered problem of distinguishing primary diabetes insipidus from nephrogenic insipidus and from psychogenic polydipsia.

The case herein reported is an example of prolonged functional depression of antidiuretic mechanisms secondary to excessive water intake and simulating primary diabetes insipidus. Reversal of this phenomenon was not obtained by the usual diagnostic methods. Adequacy of antidiuresis was finally demonstrated by the response to a large dose of nicotine. Return of normal sensitivity to fluid deprivation was demonstrated following the elimination of excessive water intake.

Case Report

A 16-year-old white male was admitted to Beth Israel Hospital in September, 1959, with a history of polyuria and polydipsia of nine months' duration. During the summer of 1958 the patient had been under considerable emotional stress. He feared that his "girl friend," who was three years his senior, would discover his true age. He encountered academic difficulties at school, and was upset by his father's illness and continued unemployment after recovery. A psychiatrist states that at this time the patient was obsessed with the need to "become bigger." In an effort to gain body bulk the patient decided to increase his food intake. By December, 1958, he felt that his weight gain had been excessive and, in order to decrease food consumption, he voluntarily began to ingest large quantities of fluid. He did not complain of excessive thirst, and had no particular preference for iced liquids. During the 14 months prior to admission the patient had increased in weight

*Received for publication March 16, 1960.

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from 145 to 205 pounds, and had increased two inches in height. He denied fatigue, weakness, headache, visual disturbances, incoördination, edema, hematuria, and dysuria. Three months prior to admission the patient developed Bell's palsy, which disappeared after two months. There was no family history of polyuria or polydipsia.

Physical examination was entirely within normal limits, as were the following laboratory studies: hemoglobin, hematocrit, white blood cell count, differential, serum electrolytes, blood urea nitrogen, cholesterol, cholesterol esters, albumin, globulin, serology, erythrocyte sedimentation rate, protein-bound iodine, glucose tolerance test, phenolsulfonphthalein excretion, and urinalysis. Twenty-four-hour urinary excretion of electrolytes, creatinine, 17-hydroxysteroids and 17-ketosteroids were within normal limits, as were the visual fields, electroencephalogram, basal metabolic rate, and x-rays of the skull and chest.

Urine output without medication varied from 8 to 12 L. daily, with a specific gravity of 1.001. Special studies for the differentiation of diabetes insipidus from psychogenic polydipsia were performed, as follows:

1. Twenty-four-hour water deprivation test.[1] All fluids were withheld for 24 hours on two occasions. During the second test period the patient was under constant observation. Urine output was 4.5 L., with a maximal specific gravity of 1.010 achieved at the end of each study. The patient lost 10 pounds during each 24-hour period of water deprivation. There was no evidence of dehydration, nor did the patient experience extreme thirst.

2. Hypertonic saline infusion test[2] (Figure 1). A slight increase in urine flow was noted during the infusion period, while a fall from 16.3 to 6.7 ml./min. occurred after the administration of 0.1 unit of aqueous Pitressin intravenously, with a corresponding rise of specific gravity to 1.012.

3. Nicotine stimulation test[3] (Figure 2). Following the administration of 5.6 mg. of nicotine salicylate (equivalent to 3 mg. of pure nicotine), no antidiuresis occurred. However, 9.3 mg. of nicotine salicylate (equivalent to 5 mg. of pure nicotine) reduced the urine flow from 12.2 to 3.3 ml./min. and raised the specific gravity to 1.008.

The patient was discharged from the hospital with instructions to limit fluid intake; concomitantly he received psychotherapy. He succeeded in voluntarily restricting fluid intake to 3 to 4 L. daily for six weeks. The patient was readmitted to the hospital in December, 1959. For five days he was maintained on a dry diet and rigid restriction of fluid to 2 L. per day. After the fifth day of normal hydration the 24-hour water deprivation test was repeated. At the end of this dehydration period the patient achieved a specific gravity of 1.016 and urine flow of 0.7 ml./min.

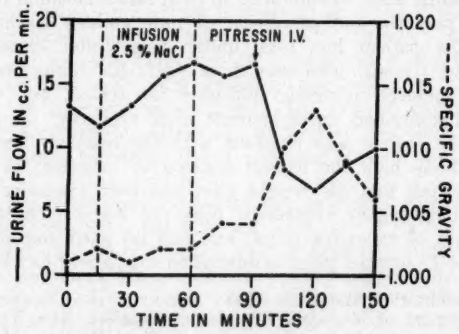

FIG. 1. Carter-Robbins test.

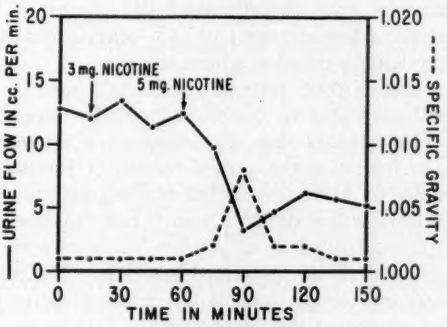

FIG. 2. Nicotine test.

At that time the osmolarity of the urine was 802 mOsm./L., and of the serum, 280 mOsm./L. The total urine output was 1,355 ml. The patient did not become severely dehydrated during the test.

DISCUSSION

Primary diabetes insipidus is caused by an insufficiency of antidiuretic hormone (ADH). It is characterized symptomatically by the usually abrupt onset of polyuria and polydipsia, with urine output approximating several liters per day. The patient experiences extreme thirst and prefers to drink iced fluids. Water deprivation is often intolerable. The polyuria results from the diminished ability of the renal tubule to reabsorb solute-free water in the absence of ADH. The nephrogenic form is most readily distinguished by the complete failure of the renal tubules to concentrate the urine after the administration of Pitressin. It becomes manifest in early childhood and, with rare exceptions, is familial.[4] In psychogenic polydipsia the renal tubules reject water because of a depression of ADH secretion, due to decreased plasma osmolarity. In the latter condition, no organic defect preventing ADH formation or action is present.

Evidence has accumulated indicating that the antidiuretic substance is formed in the supra-optic and paraventricular nuclei of the hypothalamus. It is transmitted by neurosecretory fibers to the neurohypophysis, where it is stored for release. The physiologic stimulus mediating the release of ADH appears to be an increase in plasma osmolarity. Release of ADH may also be effected by various drugs (acetylcholine and nicotine), and is part of the physiologic response to stress. Antidiuretic hormone appears to have a primary action in increasing the permeability of the distal tubule and collecting duct to the passage of solute-free water. The net result is a decrease in water excretion, with an increase in urine solute concentration, without alteration of total solute output. The ability to elaborate a urine which is hyperosmolar to plasma is considered, except in most unusual circumstances,[5] to be a function of ADH action.

Biologic methods for the direct estimation of ADH in serum and urine have met with mixed success and remain controversial.[6] Indirect tests designed to demonstrate the ability to initiate antidiuresis under standardized conditions constitute the accepted methods of indicating ADH activity. These tests include the ability to concentrate urine under conditions of (1) increased plasma

osmolarity secondary to water deprivation; (2) increased plasma osmolarity secondary to hypertonic saline infusion; and (3) stimulation of the hypothalamic-neurohypophyseal system by nicotine administration.

The diagnostic value of these tests has been challenged by the demonstration that polydipsia itself may lead to diminished tubular sensitivity to exogenous ADH.[7-9] It therefore appears that the inability to achieve antidiuresis after water deprivation, or following the administration of Pitressin, does not necessarily indicate a failure of ADH production or a permanent renal tubular defect. Dreifus et al.[10] and Barlow and de Wardener [11] have suggested that psychogenic polydipsia may be distinguished from primary diabetes insipidus by the difference in plasma osmolarity of the untreated patients. The psychogenic disorder results in a dilute plasma of low osmolarity, while diabetes insipidus produces a more concentrated plasma of high osmolarity.

During the patient's first hospital admission, the 24-hour water deprivation test gave clearly abnormal results. The efficiency of the water restriction period was attested to by the weight loss of 10 pounds during each test period. The patient's failure to achieve a maximal specific gravity above 1.010 could be interpreted as evidence in favor of primary diabetes insipidus. However, during the Carter-Robbins test the administration of 0.1 unit of Pitressin reduced urine flow from 16.3 to only 6.7 ml./min. The maximal specific gravity achieved was 1.012. These values suggest an insensitivity of the renal tubules to Pitressin.[8, 12]

The patient's response to hypertonic saline infusion was suggestive of primary diabetes insipidus, since we were unable to demonstrate antidiuresis. This false-negative response for the presence of ADH might have resulted from the patient's failure to restrict fluids for the eight-hour period prior to testing, as recommended by Carter and Robbins, or the inadequacy of this water restriction period in a chronically overhydrated subject. The resulting hypo-osmolarity of the plasma may have rendered the saline load insufficient to produce plasma hyperosmolarity of a degree necessary to elicit ADH release. It appeared possible, however, that the failure to demonstrate antidiuresis might again be related to a specific tubular insensitivity produced by chronic overhydration.

The essential integrity of the antidiuretic mechanism in this patient was indicated by the response to 5 mg. of nicotine. Nicotine administration may be a greater stimulus to antidiuresis than is the hypertonic saline infusion.[3] It apparently elicited the release of sufficient antidiuretic hormone to overcome the renal insensitivity.

The validity of the initial conclusion—that this patient had an intact neurohypophyseal system—was substantiated by the normal response to water deprivation demonstrated on his second admission to the hospital.

Summary

1. A case of psychogenic polydipsia with severe chronic overhydration is reported.

2. Water deprivation and hypertonic saline infusion tests initially suggested primary diabetes insipidus.

3. The integrity of the neurohypophyseal system was demonstrated by the administration of a large dose of nicotine and by repetition of the water deprivation test after a period of normal hydration.

ACKNOWLEDGMENTS

I wish to thank Dr. Robert Gittler for his invaluable suggestions throughout the preparation of this report, and Dr. Marvin Sinkoff for his help in obtaining the osmolarity studies.

SUMMARIO IN INTERLINGUA

Es reportate un caso de polyuria e polydipsia de un duration de novem menses in un masculo de 16 annos de etate. Le examine physic e endocrin e routinari studios laboratorial produceva valores intra le limites del norma. Initialmente le test a privation de aqua pro 24 horas e le test a infusion de solution salin hypertonic secundo Carter-Robbins pareva supportar un diagnose de primari diabete insipide. Le administration intravenose de 0,1 mg de Pitressina durante le test de Carter-Robbins produceva un antidiurese subnormal. Tamen, le stimulation del systema neurohypophysee per le administration intravenose de 5 mg de nicotina evocava un normal responsa antidiuretic. Le integritate del mechanismos antidiuretic in iste patiente esseva confirmate per le repetition del test a privation de aqua post cinque dies de restriction del consumo de liquido a 2 L per die. Es formulate le opinion que le absentia de antidiurese in responsa al tests standard de infusion de solution salin hypertonic e de privation de aqua esseva causate per un transiente insensibilitate reno-tubular al Pitressina que pote esser explicate per le hyperhydratation chronic. Le problema del diagnose differential in patientes qui se presenta con polyuria e polydipsia es discutite, con referentias particular al methodos pro le distinction inter diabete insipide nephrogene, polydipsia psychogene, e diabete insipide primari.

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REVIEW

THE ROLE OF COUNTERCURRENT MECHANISMS IN URINE CONCENTRATION: A REVIEW *

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Introduction

Within the past few years, there has been a remarkable advance in our understanding of the mechanism by which the kidney is able to produce a concentrated urine. The stimulus for this recent burst of progress has been the introduction into the field of a revolutionary new concept: that of the countercurrent osmotic multiplier. In this brief review, an attempt will be made to present the broad outlines of this new theory along with some explanation of its underlying physical principles and a summary of its major supporting evidence. No attempt will be made to treat the whole subject of the countercurrent mechanism exhaustively nor to debate *in extenso* the several still controversial aspects of the theory. Rather, the reader interested in these matters will be referred to the original literature as these points arise in the ensuing discussion.

Historic Survey

The impact which the countercurrent theory has made upon modern renal physiology can best be appreciated by viewing it in its historic perspective.

In reviewing the historic development of the various theories dealing with the concentrating function of the kidney, it is interesting to note how often this function has been linked to the loop of Henle. Such a relationship was suggested in 1907 by Peter,[1] who noted a correlation between the maximal concentration of the urine achieved by various mammals and the length of the thin segment of the loop of Henle in the kidneys of such mammals. In 1927 Crane[2] pointed out that only mammals and birds can form concentrated urine and that it is only in these phyla that thin segments of the loops of Henle occur. Closely related to this observation were the experiments of Burgess et al.,[3] which showed that it was only in birds and

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in mammals that antidiuretic hormone increased the tubular reabsorption of water. In fact, on the basis of these experiments Burgess et al. were led to the almost prophetic hypothesis that the urine was concentrated in the loop of Henle and that antidiuretic hormone had its locus of action upon this segment of the nephron.

This hypothesis, however, seemed to be invalidated by the classic studies of Walker et al. in 1940,[4] which demonstrated that the tubular urine obtained by direct micropuncture from the distal convolution of the nephron of the rat was at most iso-osmotic and certainly was not hyperosmotic as would be expected if the final concentrating operation occurred in the loop of Henle.

An alternate mechanism for concentrating the urine was that developed by H. W. Smith et al.[5, 6] In this view, the proximal tubule reabsorbed sodium by active transport, while water reabsorption in this segment was passive and secondary to the osmotic gradient generated by solute transport. The loop of Henle was thought to represent a segment where osmotic equilibration could be completed, and its thin epithelium seemed ideally suited to this function. In the distal tubule facultative solute reabsorption and facultative water reabsorption could occur, the latter being dependent upon the presence or absence of antidiuretic hormone. Final concentration of the urine to hyperosmotic levels was felt to occur in the collecting ducts. Since there seemed to be no reasonable alternative, this final abstraction of water necessary to produce hyperosmotic urine was thought to involve an active transport of water.

This hypothesis of Smith et al. was widely accepted and stimulated a great deal of work on clinical and physiologic levels. The hypothesis, however, contained the feature of active transport of water, and this has always posed considerable conceptual problems. The favorite model for active transport processes generally consists of a biochemical pump which attacks molecules or ions of the transported substance one by one and which is driven by metabolism. In the case of ions, such a concept provides a reasonable working hypothesis. However, in the case of water, the situation is different simply because the rates of water movement by the hypothetic pump would exceed by several orders of magnitude the rates of oxygen consumption.[7] Such extremely high rates of water movement occurring on a molecule by molecule basis raise virtually insuperable problems to any hypothesis explaining the link between the energy yielding reactions of metabolism and the operation of the pump.

In 1951, a bold new theory was introduced to explain the mechanism whereby the kidney concentrates the urine. The theory stemmed jointly from Wirz, Hargitay, and Kuhn,[9, 10] all of the University of Basel.* These investigators saw in the structural arrangement of the loop of Henle the possibility of the operation of a countercurrent multiplier system, the effects

* Kuhn and Ryffel[8] first proposed the theory as applied to the kidney in 1942.

of which would be to produce a gradual, progressive increase in the effective osmotic pressure of the fluids of the loop of Henle (and the adjacent interstitial fluids of the renal medulla) along the long axis of the loop (i.e., from the corticomedullary junction to the tip of the papilla). Concentration of the final urine was then conceived to occur in the collecting ducts through a passive withdrawal of water from the fluid in these structures as they traverse the progressively more hypertonic medullary interstitial fluid (Figure 1).

The countercurrent feature of the system was seen as a means whereby the loop of Henle could achieve the high osmolalities required to produce highly concentrated urine, while avoiding any large osmotic gradients across

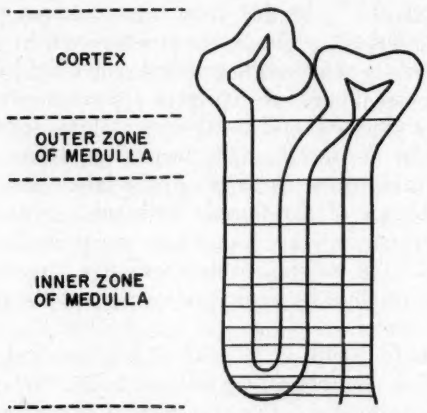

FIG. 1. The increase in osmolality of the renal medulla predicted by the countercurrent theory is depicted by the increased density of lines. Note that the glomeruli, the proximal and the distal tubules are cortical in location, while the loops of Henle and the collecting ducts are medullary structures.

a single cell membrane. In order to understand the details of how this might come about it is useful to discuss some simple models which illustrate the principles of countercurrent systems.

PRINCIPLES OF COUNTERCURRENT SYSTEMS

The basic feature of a countercurrent system is that two streams of fluid moving in opposite directions become so juxtaposed as to exchange energy or material in accordance with the forces acting upon them.[11] Countercurrent systems of this type may operate in one of two ways—as countercurrent exchangers or as countercurrent multipliers.

Figure 2 illustrates a model of a countercurrent exchanger in which heat is being exchanged.[11, 12] One stream of fluid enters the system in the upper portion of the left limb with a temperature of 10°C., while another

stream, flowing in the opposite direction, enters the lower portion of the right limb with a temperature of 1°C. As the warm stream of fluid flows downward, it becomes progressively cooler due to the transfer of heat to the cooler stream, which is progressively warmed. In this particular example the fluid which leaves the system does so at a temperature of 9°C. Note that although the overall temperature change experienced by either stream is eight degrees, there is no temperature gradient anywhere between the two streams of greater than one degree.

This particular type of system is rather widely encountered in biology. One of the most striking examples occurs in the circulatory systems of various arctic animals whose extremities are exposed to low ambient tem-

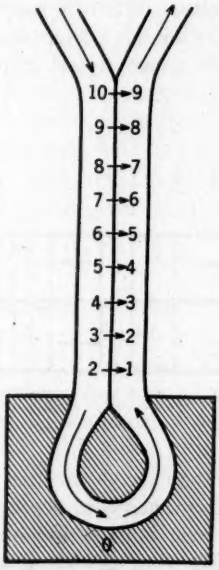

FIG. 2. Countercurrent heat exchanger (after Scholander [11, 12]).

peratures. Conceivably the circulation of blood at body temperature through such extremities could impose a serious drain on bodily heat. This problem is neatly circumvented by a countercurrent exchanger of exactly the type depicted above. Heat of the arterial blood is used to warm the venous blood coming from the extremity. Anatomically this heat exchange between arterial and venous streams occurs in a highly specialized vascular network known as a *rete mirabile*. This structure consists of a number of small vessels carrying the arterial blood which are intimately intermingled with other small vessels carrying the venous blood. As the warm arterial blood flows through the *rete mirabile* it loses heat to the cool venous blood

flowing in the opposite direction. This system basically represents a "short-circuit" for heat by which blood profusing the extremities is cooled, thereby minimizing heat loss to the environment.

This countercurrent exchanger system may be contrasted to a countercurrent multiplier system, a model of which is illustrated in Figure 3. This model, after Hargitay and Kuhn,[9] consists of an osmometer in the form of a loop, the two limbs of which are separated by a semipermeable membrane, but connected to each other by a thin capillary loop. Flow of a solute-containing fluid through the system is maintained by a fixed hydrostatic pressure, P, from the reservoir connected to one end of the upper limb. The hydrostatic pressure is uniformly transmitted to the upper limb until the point of reversal is reached. At this point it is abruptly reduced because of the resistance offered by the capillary loop. As a result of the hydrostatic pressure, water is "squeezed" through the membrane, and the solute is progressively concentrated, reaching a peak concentration

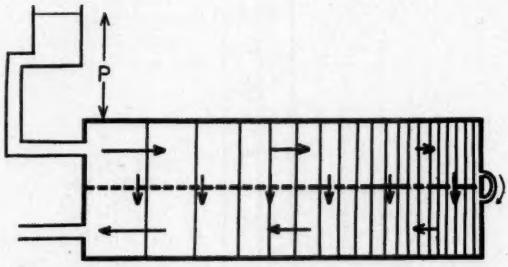

FIG. 3. Countercurrent osmotic multiplier (after Hargitay and Kuhn[9]). The progressive density of the lines represents the increasing concentration of the solute.

at the reversal point. This highly concentrated fluid now enters the lower limb via the capillary loop and undergoes a progressive dilution as it flows out of the system. In the steady state the fluid which leaves the system has the same osmotic pressure (i.e., the same solute concentration) as the fluid which enters.

The whole system can be looked upon as an arrangement of successive single osmometers, each of which operates with a small, fixed hydrostatic pressure. Each single osmometer alone can effect only a slight concentration of the solute. But by the successive arrangement of such single osmometers, the fluid concentrated by the first osmometer can then be acted upon sequentially by the second and then by the third, and so forth, until a very considerable concentration can be achieved. The countercurrent multiplier operates in just such a fashion except that the arrangement is a continuous, rather than a discontinuous, series of individual steps or "single effects." Each single effect may indeed be very small, but when superimposed upon all the accumulated single effects already achieved, a very

large overall effect results. The result is basically a multiplication of the single effect and the system is therefore referred to as a countercurrent multiplier.

Although this particular model is useful in explaining the principle of countercurrent multipliers, it needs to be modified to become a more accurate model for the loop of Henle. Instead of hydrostatic pressure, the kidney uses active transport as the driving force. And instead of moving water, the loop of Henle moves solute, specifically sodium chloride, while restraining water (see below). It makes no basic difference to the theory that the opposing limbs of the loops of Henle are not in direct contact, so long as the opposing membranes of the two limbs have the requisite permeability properties with respect to water and solute, and so long as the distances involved between the two limbs of the loop are microscopic.[13] When these two conditions are met, the medullary interstitial fluid surrounding the two limbs of the loop will also be concentrated in a manner similar to that occurring in the fluids within the loops themselves. With these modifications the model becomes a more realistic one in terms of similarity to the loop of Henle and will operate in a fashion so as to create the longitudinal increase in osmotic pressure in the medullary fluids required for the withdrawal of water from the collecting ducts as they traverse this area.

Evidence for the Countercurrent Theory

Three types of evidence implicate the operation of a countercurrent system in the concentrating mechanism of the kidney. The first line of evidence consists of measurements by Wirz, Hargitay, and Kuhn[10] of the osmolality of the tubular fluids in various regions of the kidney. In these experiments the freezing point of the fluids (a measure of osmolality) within the tubules was determined microscopically in unfixed microscopic sections cut at various levels of the medulla. The results showed that there was indeed a progressive increase in the osmolality of the fluids within the medullary tubules, with the highest values occurring in sections taken from the tip of the papilla. The osmolality of the fluids of the cortical structures, on the other hand, was practically the same as that of plasma. Despite the marked increases in osmolality occurring along the long axis of the loops of Henle in the renal medulla, Wirz et al.[10] did not discern any differences in osmolality between the fluids in the limbs of the loops of Henle and the collecting ducts *in any one transverse section.* The conclusion, therefore, was drawn that the kidney during antidiuresis was composed of concentric shells of increasing osmolality (Figure 4). The outer shell consisted of the cortex and was iso-osmotic with the peripheral plasma. Each concentric inner shell in the medulla, however, had a higher osmolality than the one outside of it, with the innermost, smallest shell at the papillary tip having the highest osmolality of all.

A second line of evidence consists of the results of chemical analysis of

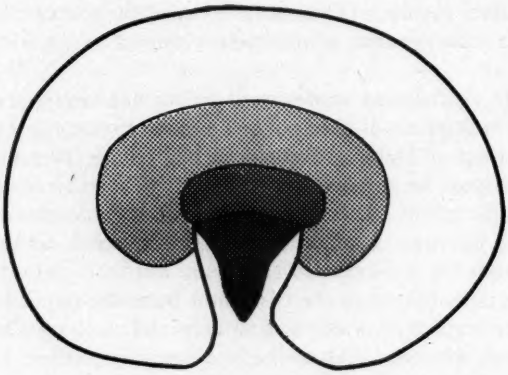

FIG. 4. Concentric shells of increasing osmolality in the antidiuretic kidney (after Wirz et al.[10]).

various portions of the antidiuretic kidney for sodium and chloride.[14] The general plan of these experiments has been to measure the sodium and chloride content of successive transverse slices of the renal medulla taken from animals in the antidiuretic state. Such studies have shown that there are increasing amounts of sodium and chloride per unit of total tissue water as one proceeds from the corticomedullary junction toward the tip of the papilla. (Figure 5) The absolute values for the concentrations of these ions probably do not accurately reflect the concentrations in the renal medul-

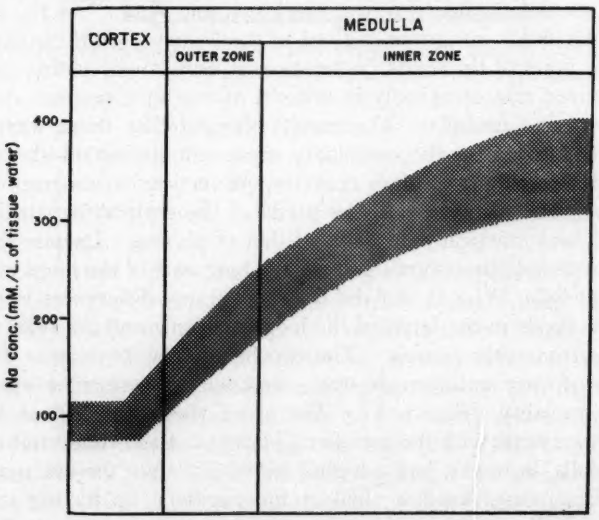

FIG. 5. Concentration of sodium in total tissue water of slices of kidney tissue of antidiuretic dogs (adapted from data of Ullrich and Jarausch[4]).

lary interstitial fluid because of the uncertain contribution of the urine trapped within the collecting ducts. The general conclusion, however, is inescapable: sodium and chloride are present in progressively increasing concentrations in the fluids of the renal medulla during antidiuresis, in full accord with the countercurrent theory. A further piece of supporting evidence is the finding of Ullrich and Jarausch[14] of a good linear relationship occurring between sodium concentration in the tip of the renal papilla and the final osmolality of the urine. This would be expected if the hypertonicity of the renal medullary fluids is due to an accumulation of sodium and chloride.

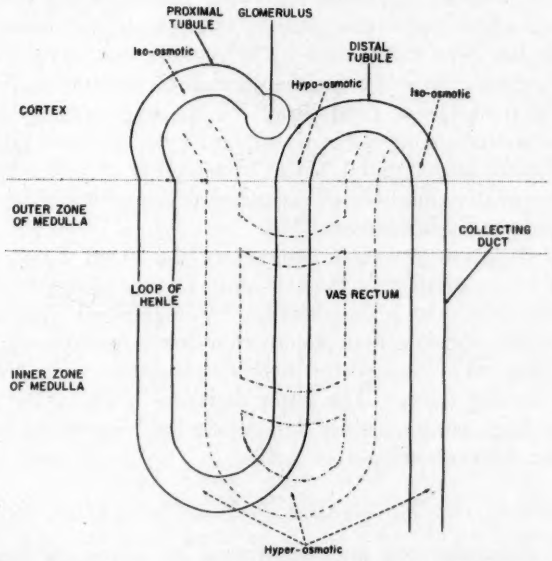

FIG. 6. Summary of micropuncture studies of osmolality in various portions of nephron during antidiuresis (adapted from data of Walker et al.,[4] Wirz,[15, 17] and Gottschalk and Mylle[16]).

A third line of evidence implicating the countercurrent system consists of measurements of the osmolality of the tubular fluid obtained by micropuncture from various portions of the nephron. Walker et al.[4] in their studies of the mammalian nephron showed by micropuncture that fluid obtained from the first two-thirds of the proximal tubule was iso-osmotic with the peripheral plasma, a finding which has been extensively confirmed in recent years by Wirz[15] and by Gottschalk and Mylle[16] (Figure 6).

In contrast to the iso-osmotic character of the fluid of the proximal tubule, fluid obtained from the tips of the loops of Henle or blood obtained from the tips of the vasa recta has been found to be highly concentrated.[16, 17] Not only are these fluids hyperosmotic, but they seem to be equal in

osmolality both to each other and to the fluid obtained from the adjacent collecting ducts of the same animal at the same time (Figure 6). This evidence is most crucial for the countercurrent hypothesis, since it is a direct demonstration of the fact that highly concentrated fluid does indeed exist in the tips of the loops of Henle as well as in the medullary interstitium, the latter being reflected by the blood in the vasa recta.

In the distal convolution, on the other hand, fluid obtained from the earliest accessible portion (which is about one-third of the total length of the convolution) has been shown to be consistently hypotonic [15, 16] (Figure 6). This hypotonicity of the early distal fluid is seen during hydropenia as well as during solute diuresis and water diuresis. It is especially marked during solute diuresis where hypertonic sodium chloride is the loading solute, a finding which has been interpreted by Gottschalk and Mylle [16] to indicate that the mechanism responsible for the dilution of the fluid in the ascending limb of the loop of Henle (and hence for the hypertonicity of the renal medulla) is a sodium pump directed outward from the loop rather than an oppositely oriented water pump, since "if secretion of water into the loop were the sole operative mechanism, its extent would probably be independent of the nature of the solutes present." [16]

Although the most proximal portion of the distal fluid is hypotonic during antidiuresis, samples of fluid obtained farther along the distal tubule are found consistently to be iso-osmotic,[15, 16] suggesting that water movement is relatively quicker than solute movement in this segment of the nephron (Figure 6). Apparently in this iso-osmotic state, the fluid now enters the collecting ducts. The latter therefore must be the site for the final concentrating operation, since iso-osmotic fluid enters and hyperosmotic fluid leaves as the final urine.

Operation of the Mechanism for Concentrating the Urine

Figure 7 illustrates one possible scheme by which the nephron could produce concentrated urine from glomerular filtrate.[18] As the result of the classical work of Richards et al., [4, 19] it is universally agreed that the glomerular filtrate is iso-osmotic with the parent plasma, and has a concentration of 300 mOsm./Kg. of water (Figure 7). During passage through the proximal tubule, the glomerular filtrate undergoes a major diminution in volume so that about 80 to 85% of the original volume is reabsorbed. It is generally, but not universally,[20] agreed that this proximal reabsorptive operation involves active transport of sodium with water following passively as the result of the osmotic gradient created by the reabsorption of sodium (and its anions). The overall reabsorptive operation is therefore an iso-osmotic one.

The tubular fluid now enters the descending limb of the loop of Henle and becomes concentrated during its descent due either to a gain of sodium, a loss of water, or both. At the tip of the loop, the fluid is highly concen-

trated. It now traverses the ascending limb where it becomes progressively diluted, ultimately entering the distal convolution in a hypo-osmotic state. There is some uncertainty about the detailed operations of the loop, since there are several possible variations of the basic countercurrent mechanism which could explain the available data. It is perhaps useful in this connection to point out the minimal requirements which are necessary to explain the evidence. These requirements concern primarily the properties of the ascending limb of the loop. For the system to work at all, this segment must be relatively impermeable to water and must have an out-

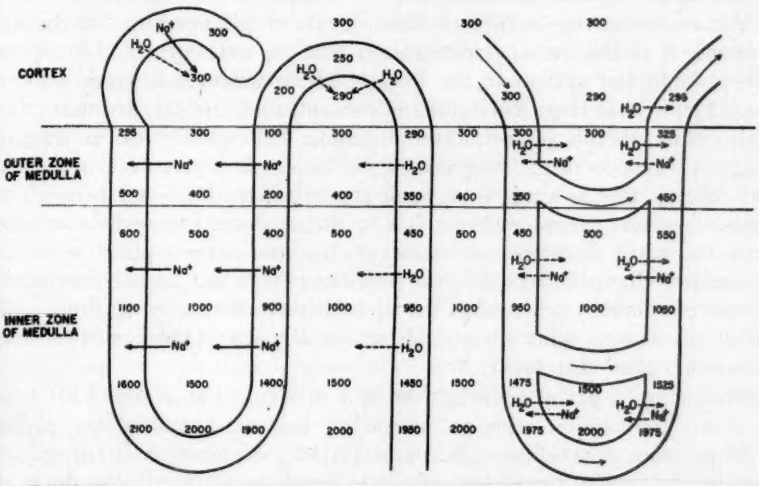

FIG. 7. Possible scheme for concentrating the urine during antidiuresis (see Winters and Davies [18]). The vas rectum has been removed to the right for the sake of clarity. The numbers indicate the osmolalities of various fluids, with 300 mOsm. being taken as the value of peripheral plasma. In this scheme, the final urine is about 2,000 mOsm./Kg. water, a value which could be the case in the rat. All active transport processes are indicated by solid arrows; passive processes are indicated by dashed arrows. The sodium pump of the loop of Henle is arbitrarily assumed to be able to develop a concentration difference of 100 mOsm. All values for osmolality shown represent steady state values and not equilibrium values. Water movements from the cortex into the blood are shown for the sake of simplicity as occurring into the effluent of the vas rectum (see text).

wardly directed sodium (or chloride) pump. The descending limb, on the other hand, can have a variety of properties so long as it is not impermeable to both sodium and water. Given these minimal requirements, the whole system can act as a countercurrent multiplier and can produce hyperosmotic interstitial fluid. Sodium chloride is pumped out of the ascending limb while water is restrained; this produces an increase in the sodium concentration of the interstitium. The iso-osmotic fluid entering the descending limb from the proximal tubule increases its sodium concentration as it encounters the progressively more hyperosmotic interstitium. This could be due either to diffusion of sodium inward, diffusion of water outward,

or both, or it could be due to an active transport of sodium inward. In the formulation of Gottschalk and Mylle[16] the descending limb is conceived to be entirely passive with respect to both sodium and water. Smith,[21] on the other hand, has objected to this idea, since it invokes quite different functional properties to two limbs of the loop of Henle which appear to be so similar structurally. One way to meet this objection is to suppose that the descending limb is also relatively impermeable to water and that it transports sodium inwardly by an active transport mechanism. In this formulation (Figure 7) the two limbs of the loop would differ functionally only in the direction of the active sodium transport.

Whatever the true nature of these details of the operation of the loop of Henle, it is clear in any formulation that the existence of the countercurrent multiplier system in the loop of Henle achieves a great theoretic advantage, in that large differences in concentration are avoided across any single cell membrane, yet a substantial osmotic concentration can be achieved along the direction of the long axis of the loop. Any given cell in the loop need only be able to establish a small concentration difference between the tubular fluid and the interstitium, but by virtue of the counterflow arrangement, the small difference so achieved becomes superimposed upon the accumulated changes effected by the previous cells, and a large concentration difference is thereby achieved at the tip relative to the incoming fluid. The overall situation is quite comparable to the analogy of the series of single osmometers alluded to earlier.

Following its passage through the loop of Henle, the tubular fluid enters the distal convolution with an osmolality less than that of the plasma. In the presence of antidiuretic hormone (ADH)—a nearly absolute requirement for the production of hyperosmotic urine—water can move down the osmotic gradient between the tubular fluid and the iso-osmotic cortical fluids. This movement of water must necessarily dilute some portion of the cortical fluids (Figure 7), the exact extent being dependent upon the size of the pool of cortical fluid involved, the rate of acquisition of water from the tubules, and the rate at which water moves into the blood. As a result of this loss of water, the fluid in the distal tubule is now much reduced in volume and again is iso-osmotic. It then enters the collecting duct. These structures course straight down through the hyperosmotic medulla and, in the presence of ADH, water moves passively into the interstitium and hyperosmotic urine is formed.

The urine having been concentrated, it is now necessary to explain how the water and the sodium which are reabsorbed can be returned to the general circulation. This function is performed by a specialized set of capillaries known as the vasa recta, which provide the circulation for the renal medulla. These capillaries originate from efferent arterioles of juxtamedullary glomeruli and dip down into the medulla forming hairpin loops which are in close approximation with the loops of Henle. Longley et al.[22]

have recently studied the fine structure of the ascending and descending limbs of the vasa recta and have pointed out that their anatomic arrangement is rather similar to the arrangement encountered in various *retia mirabilia,* in that any one descending limb tends to be surrounded by ascending limbs while any given ascending limb is surrounded by descending limbs. Another interesting and possibly important anatomic feature of the vasa recta is that they are provided with anastomatic cross-connections between the two limbs of the loop.

If it is assumed that the vasa recta have permeability properties similar to those of capillaries elsewhere in the body, then they can operate as countercurrent exchangers (Figure 7). Iso-osmotic blood enters the vasa recta, and as it encounters the increasingly hyperosmotic medullary interstitium, it gains sodium and loses water, so that at the tips of the vascular loops it is highly concentrated. During ascent of the loop, the blood undergoes a progressive dilution through a gain of water and a loss of solute. This countercurrent feature of the vasa recta allows blood to circulate through the renal medulla with minimal dissipation of the hyperosmolality of the interstitium. It should be emphasized that the passive nature of the vasa recta precludes them from making the mechanism more efficient in the sense that they could "boost" the osmolality of the interstitium to a value higher than that achieved by the loop of Henle alone. The vasa recta, however, do make the multiplier more effective compared to a comparable system receiving a through-and-through type of blood flow, since the countercurrent exchanger nature of the vasa recta permits a more complete equilibration of the blood with its environment.

One major factor controlling the extent of equilibration achieved by the blood is the rate of blood flow.[23] A low rate of flow would favor more complete equilibration and hence would preserve medullary hypertonicity. A rising rate of blood flow increasingly yields a through-and-through type of flow which could literally wash away the solute and hence dissipate the high osmolalities created by the loop of Henle. It seems probable that the anastomotic cross-connections, known to be present between the two limbs of the vascular loops, would function to short-circuit much of the total flow from one limb to the other, thereby reducing the effective blood flow at the tip of the vascular loop and so help to preserve the hyperosmolality of the interstitium and the loop of Henle.

It is virtually certain that the blood in the vasa recta never achieves complete osmotic equilibration with its surroundings. Indeed, there is a theoretic necessity for assuming that the blood as it leaves the renal medulla is slightly hyperosmotic compared to that which enters the medulla (Figure 7). If this were not the case, the sodium which is reabsorbed by the loop of Henle would not be removed, and the total body sodium would end up in the renal medulla!

The final step involves the removal of water which is reabsorbed from the

distal tubule. Conceivably this occurs by a passive movement of water from the cortical fluids into the virtually iso-osmotic blood * perfusing that portion of the cortex. This movement must dilute that particular blood to some osmolality less than that of the peripheral plasma. The mixing of this blood with the hyperosmotic blood from the medulla leads to a final osmolality for the total renal venous blood which is slightly less than that for the renal arterial blood. It is of course obvious, although sometimes forgotten, that when hyperosmotic urine is formed from iso-osmotic renal arterial blood, the renal venous blood must be hypo-osmotic. Thus, whereas the urine is first concentrated, then diluted, and then reconcentrated, the blood is first concentrated and then diluted. Blood leaves the outer medulla slightly concentrated, but it becomes hypo-osmotic in the cortex and leaves the kidney in this state.

Some Outstanding Questions

While the countercurrent theory provides a satisfactory explanation for concentrating the urine, it also poses a number of additional questions, none of which has been answered in a completely unequivocal manner.

How Is the Urine Diluted? Numerous suggestions have been made to explain the mechanism by which the urine is diluted. The simplest explanation would be that the countercurrent multiplier continues to operate, but that in the absence of ADH, water permeability of the distal tubule and of the collecting duct is considerably reduced. In this view, the hypo-osmolality of the fluid entering the distal convolution from the loop is preserved throughout the passage of the more distal portions of the nephron and appears as the final dilute urine. Hence the basic mechanism responsible for dilution resides in the loop of Henle, particularly in that segment responsible for the production of the hypo-osmotic fluid entering the distal convolution. In this view, ADH need exert a permissive effect only upon the water-permeability properties of epithelium, a role consonant with its effect upon water movements in the frog's skin.[24]

There is some evidence to support this general view of the mechanism for dilution. First, from the ingenious experiments of Berliner et al.,[25] it is known that the urine can be concentrated even in the absence of ADH. These workers were able to effect an abrupt reduction in the rate of glomerular filtration in one kidney of a dog undergoing a water diuresis; by this maneuver they obtained hyperosmotic urine from the ipsilateral side, while urine from the contralateral side remained dilute. These results could be interpreted to indicate that the medullary interstitial fluid was hyperosmotic and that with sufficient reduction of tubular urine flow in the collecting ducts (through reduction of the glomerular filtration rate and hence a greater reabsorption proximally), water movement occurred from the ducts into the medullary interstitium, thereby concentrating the urine.

* Actually, this cortical blood will be slightly hyperosmotic due to slight increase in colloidal osmotic pressure.

A second line of evidence suggesting that the countercurrent multiplier continues to operate during water diuresis consists of the results of chemical analyses of the medulla for sodium. When expressed in terms of total tissue water these results are very difficult to interpret, since the contribution of trapped dilute urine to the total tissue water is likely to be substantial. However, when the data are expressed in terms of dry weight [23] the sodium content of the medulla approaches that seen during antidiuresis.

The third line of supporting evidence consists of recent experiments of Bray,[26] who showed in experiments similar in design to those of Wirz et al.[10, 15, 17] that during water diuresis hyperosmotic fluid was present in the loops of Henle, whereas hypo-osmotic fluid was present in the collecting ducts.

Obviously the most direct and unequivocal evidence to support the idea that the countercurrent multiplier continues to operate during water diuresis would be a demonstration that fluid obtained by micropuncture from the tips of the loops of Henle and blood obtained from the tips of the vasa recta were hyperosmotic while the final urine being formed was hypo-osmotic. Thus far no experiments of this type have been published.

Alternative or ancillary points of view concerning possible mechanisms of water diuresis are possible. ADH may not only affect the water-permeability properties, but may also increase the sodium transport by the loop, a suggestion in accord with the action of this hormone in the toad's bladder.[27] Hilger et al.[28] have demonstrated that sodium reabsorption can occur in the collecting ducts. Although it is difficult to integrate this finding into any sort of a countercurrent mechanism, sodium reabsorption at this site could play a role in dilution. Indeed, Wirz' data [15] suggest that the collecting ducts may effect a further dilution of the already hypo-osmotic fluid entering them during water diuresis. Finally, changes in the rate of medullary blood flow (see below) could exert considerable effect upon the efficiency of the countercurrent multiplier system, and conceivably such changes in blood flow could be of physiologic significance in the mechanism of urinary dilution.

How Is Urea Handled? Urea appears to play a unique role in the concentrating mechanism. It is well established that the urine can be concentrated to a higher level osmotically when urea is a major solute than when it is not.[29, 30] Furthermore, during antidiuresis, there is a progressive increase in the concentration of urea in transverse slices of the medulla as one proceeds from corticomedullary junction to the tip of the papilla.

Two different hypotheses have been advanced to account for these findings. Schmidt-Nielsen [31] has suggested that urea may be actively transported and may participate in a countercurrent multiplier system similar to that for sodium in the loop of Henle. This could account for the high concentrations of urea in the medullary interstitium, and the urea so concentrated could enter the collecting ducts by passive diffusion (or active trans-

port). This hypothesis involves the postulation of active transport for urea for which there is a precedent in the frog's kidney.[32]

An alternate hypothesis is that of Levinsky and Berliner,[30] who believe all of the observations can be accounted for by passive movement of urea. In this view, during antidiuresis the urea of the tubular fluid entering the collecting duct diffuses back into the medullary interstitium along a concentration gradient created by the withdrawal of water as the urine is concentrated. According to the data of these investigators, the concentration of urea in the medullary fluids is from 60 to 90% of the urea concentration in the final urine. Hence, most of the urea and the osmolality contributed by it in the final urine is balanced osmotically by urea in the interstitial fluid, leaving only the small remainder to be balanced by sodium and chloride of the medullary interstitial fluid. This hypothesis could then explain the increases in the medullary urea content and the concentrating of urea to higher levels than in the case of other solutes.

What Is the Importance of Alterations in Medullary Blood Flow? In the foregoing discussion, it was pointed out that the rate of blood flow through the vasa recta can exert a critical influence upon the efficiency of the countercurrent multiplier of the loop of Henle in creating and maintaining hyperosmolality of the medullary interstitium. Alterations of medullary blood flow therefore are of potential importance physiologically, pharmacologically, and pathologically in conditioning the behavior of the concentrating mechanism. All such possibilities are, however, speculative and will remain so until precise methods become available for the measurement of medullary blood flow.

Conclusions

The theory of a countercurrent mechanism for concentrating the urine offers a number of attractive features. First, it provides a reasonable explanation as to how the urine may be made hyperosmotic, while all water movements remain passive and secondary to active solute movements. Postulation of active water transport is therefore avoided. The fact that the kidney produces concentrated urine by first concentrating the tubular fluid, then diluting it, and then reconcentrating it, while seemingly an inefficient mechanism, may be only a reflection of the geographic separation of the bulk of sodium reabsorption (in the medulla) from the bulk of the water reabsorption (in the cortex) necessary to produce concentrated urine if no mechanism is available for active water reabsorption.

Second, the feature of the countercurrent multiplier avoids postulating the existence of large concentration differences across single cell membranes * and yet makes possible the achievement of large concentration differences in the tip of the papilla relative to the cortex. Hyperosmolality is

* Such a mechanism allows high efficiency in the utilization of metabolic energy in that large numbers of ions could be concentrated to low gradients for any given amount of energy. A mechanism for such a biologic potential divider has been published.[33]

therefore not established by one gigantic step but by the successive accumulation of many very small steps.

Third, the countercurrent theory allows a rational explanation for the structure of the loop of Henle and provides another impressive example of the interdependence of structure and function.

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EDITORIALS

PREREQUISITE OF FREEDOM: A HYPERTONIC URINE

In this issue of the Annals appear four papers that illustrate the complementary roles of basic science and clinical medicine. One paper examines the effect of the antidiuretic hormone, vasopressin, on the mechanisms of solute and water transport in the bladder wall of the toad. A second reviews the elegant countercurrent exchanger and multiplier system that results from the special configurations and functions of nephrons and capillaries of the mammalian kidney; it is in this system that vasopressin facilitates the elaboration of a hypertonic urine. And the third and fourth present the clinical problem of the patient with polyuria and polydipsia. The biochemical and physiologic data in the first two papers help to elucidate this clinical problem as set forth in these latter studies; and all these papers exemplify the debt of medicine to comparative physiology.

The evolution over geologic time of the mechanisms for the regulation of water metabolism may seem a far cry from clinical medicine. Yet the physician's understanding of the patient with diabetes insipidus is enhanced by some knowledge of these evolutionary steps. When the first reptile crawled out of the sea in the arid Permian period some two hundred million years ago, his immediate physiologic need in that particular Garden of Eden was to conserve water. In face of this need on the dry land and in the air, the uric acid metabolism of reptiles and birds was a great advantage; the fact that uric acid could be more highly concentrated than urea and could be excreted in the semi-solid state permitted a high degree of conservation of water. In birds the development of the first truly hypertonic urine was especially important, for they were the first creatures to develop the warm-blooded state that requires dissipation of body heat by vaporization of water. Thus, a hypertonic urine was a prerequisite of this early emancipation from the aqueous environment of the sea.

A prior and unsuccessful bid for the same freedom had been made a mere one hundred million years before in the late Devonian period. Then the first primitive amphibian, floundering from puddle to puddle, evolved a water-permeable skin that actively pumped in sodium to hold the water soaked up intermittently from an environment where water was in short supply. But this was not enough and amphibians, alternating between desiccation and overhydration, are still tied to the watery world whence they came. The early terrestrial mammals, springing from the same stock as reptiles and birds, likewise achieved physiologic freedom by evolving the ability to excrete a hypertonic urine. But mammals retained a metabolism in which urea was the end product; and urea requires more water for its excretion than does uric acid. The key features of the mammalian kidney that developed to

meet this need consisted of glomeruli and long looped tubules that permitted the filtration and reabsorption of large volumes of fluid and the final excretion of less water than solute. This was a critical step in the course of evolution "from fish to philosopher." [1]

There is a factor common to all these evolutionary attempts to achieve physiologic freedom over the last three hundred million years. This is the action of certain neurohypophyseal peptides on the permeability to water of various epithelial tissues. In man the neurohypophyseal "antidiuretic hormone" has been identified by du Vigneaud and co-workers [2] as arginine vasopressin; its chemical structure consists of eight linked amino acids of which phenylalanine is the third and arginine is the eighth amino acid. The same peptide is secreted as the antidiuretic hormone in most other mammals except the pig; in the pig it is lysine vasopressin (in which lysine replaces the arginine). In other nonmammalian vertebrates (birds, reptiles, amphibians) the neurohypophyseal peptides are different structural analogs: oxytocin (3-isoleucine, 8-leucine) and arginine vasotocin (3-isoleucine, 8-arginine vasopressin). As Sawyer, Munsick, and van Dyke show in their recent review of the comparative pharmacology of antidiuretic hormones,[3] analogous neurosecretory systems in vertebrates go back phylogenetically to fresh water teleosts or bony fish, an evolutionary stage that long preceded the adaptive need to conserve water. In these fish arginine vasotocin served no known function, but subsequently, when water conservation became an evolutionary necessity, "an ancient molecule was put to a new use." [3] This use was to increase the permeability of certain epithelial tissues to water in a direction that favored its conservation by the organism; in the skin and the bladder wall of amphibians, in the renal tubules of birds and mammals.

The common action of the neurohypophyseal peptides on these several tissues permits the use of the frog skin and toad bladder as in vitro laboratory models for study of the biochemical action of arginine vasopressin, the antidiuretic hormone of man. The primary action of vasopressin in these tissues is to increase their permeability to water and urea, with a secondary and lesser effect on the active transport of sodium.[4] The biochemical mechanism of the increase in permeability has been clarified recently by Schwartz and his colleagues.[5] Using tritium-labeled arginine vasopressin, these workers have shown that the binding of the hormone to receptor sites

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in the mammalian renal tubule and in the toad bladder involves a disulfide-sulfhydryl interchange reaction; they postulate that this reaction produces conformational changes in the proteins of the membrane barrier, changes permitting the more rapid passage of molecules of water. Hays and Leaf, as presented in this issue, have employed the toad bladder to study the phenomenon of vasopressin insensitivity that occurs in certain types of overhydration and in potassium deficiency. Their in vitro observations suggest that in the former, dilution of the body fluids has a direct effect on the permeability of the tissue and its response to the hormone, whereas in the latter the effect is mediated through the action of vasopressin on the active transport of sodium. Nevertheless the main action of the antidiuretic hormone, vasopressin, in the mammalian kidney is to control the permeability to water of certain segments of the renal tubule to the end that a hypertonic urine may be formed.

The recent concept of the mammalian kidney as a countercurrent exchanger and multiplier for the formation of a hypertonic urine is set forth in this issue by Winters and Davies. In the first development of this concept Hargitay and Kuhn [6] borrowed heavily from the field of engineering. Indeed these engineering principles have been found to function widely in the whole field of biology, as Scholander has shown.[7] The great blue heron, wading in icy winter waters, is protected from chills by the efficient countercurrent heat exchanger that functions in the veins and arteries of his legs and feet; there is a similar countercurrent heat exchanger in the fin of the whale. A countercurrent oxygen exchanger functions in the swim-bladder of the deep sea wreckfish, in the gill of the teleost fish, in the placenta of many mammals. And the principle of the countercurrent multiplier is operative in the avian and mammalian kidneys for the purpose of building osmotic gradients to effect the movements of water essential to the production of a hypertonic urine.

But what are the clinical implications of a hypertonic urine? Physicians have long recognized diabetes insipidus as a disease entity characterized by the excretion of large volumes of nonsaccharinous dilute urine in the absence of renal disease. It is due to inability to secrete adequate amounts of antidiuretic hormone, the result of lesions of the posterior pituitary and supraoptico-hypophyseal region. The syndrome first was described by Frank in 1794 and needs no further elaboration here. It is enough to note that the patient's freedom of action is curtailed and his life made miserable by the copious and pathologic excretion of a hypotonic urine leading to a compelling and unending thirst. Nevertheless, a clear understanding of the diagnostic difficulties of diabetes insipidus requires consideration of some of the recent work on the physiologic mechanisms that regulate the turnover of water.

[6] Hargitay, B., Kuhn, W.: Das multiplikations-prinzip als grundlage der harnkonzentrierung in der niere. Z. Elektrochem. **55**: 539, 1951.

[7] Scholander, P. F.: "The wonderful net." Sci. Amer. **196**: 97–107, April, 1957.

In 1947, Verney, in the Croonian Lecture,[8] presented evidence for the existence in the anterior hypothalamus of receptor sites sensitive to slight changes in the osmotic concentration of the bathing extracellular fluids, receptors that govern the lease of antidiuretic hormone accordingly. How this hormone acts on the kidney to control the excretion of water has already been discussed. But the simplicity of this self-correcting physiologic servomechanism is deceptive on at least two counts. First, the hypothalamic control of the release of antidiuretic hormone is responsive to other than osmotic stimuli: to changes in fluid volume in various parts of the body, to drugs and anesthesia, and to signals from higher levels in the brain. Hyponatremic (hypo-osmotic) states due to "inappropriate" secretion of antidiuretic hormone have been described recently in patients with pulmonary and intracranial disease.[9, 10] And second, thirst and the complexities of the regulation of water intake compound the problem of regulation of total water balance. That this is a complex problem is attested by the erudite monograph by Wolf [11] on the subject of thirst, a fascinating exploration of the jungle of dipsologic lore and scientific knowledge. It is clear that thirst is controlled at least in part by an integrated hypothalamic center that likewise is susceptible to stimuli other than those of osmotic origin. Hence we have the differential diagnostic problem of separating the compulsive water drinker (one type of primary polydipsia) from the obligatory water excreter (primary diabetes insipidus). This is the clinical version of the ancient conundrum of which comes first, the chicken or the egg; does the patient urinate because he drinks or drink because he urinates? This differential diagnosis is further complicated by the fact that in diabetes insipidus the block to the release of antidiuretic hormone may be partial rather than complete [12] and by the observation that prolonged and excessive drinking in diabetes insipidus as well as in primary polydipsia will diminish the sensitivity of the kidney to the hormone.[13, 14]

The papers by Dies, Rangel, and Rivera and by Wedeen in this issue consider the above diagnostic complexities in a clinical setting. Despite the use of the more modern method of calculating free water clearances, they, as others before them, find the differential less than simple. The time-honored

[8] Verney, E. B.: Croonian Lecture: Antidiuretic hormone and the factors which determine its release. Proc. Roy. Soc. (Biol.) **135**: 25–105, Dec., 1947.

[9] Schwartz, W. B., Bennett, W., Curelop, S., Bartter, F. C.: Syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Amer. J. Med. **23**: 529–542, Oct., 1957.

[10] Goldberg, M., Handler, J. S.: Hyponatremia and renal wasting of sodium in patients with malfunction of the central nervous system. New Engl. J. Med. **263**: 1037–1043, Nov. 24, 1960.

[11] Wolf, A. V.: Thirst: physiology of the urge to drink and problems of water lack. Charles C Thomas, Springfield, Ill., 1958.

[12] Kourilsky, R.: Le diabète insipide humain. Ann. de Med. **48**: 288, 1947.

[13] Kleeman, C. R., Maxwell, M. H., Witlin, S.: Functional isosthenuria. An isolated reversible renal tubular defect. Arch. Intern. Med. **101**: 1023–1028, June, 1958.

[14] Barlow, E. D., de Wardener, H. E.: Compulsive water drinking. Quart. J. Med. **28**: 235–258, April, 1959.

dehydration test [12, 15] of itself is inadequate as well as distressing to the patient, if not dangerous. The infusion of hypertonic salt, as originally promulgated by Hickey and Hare,[16] is not completely reliable because of variability in response according to the rate and degree of the stimulus—as Díes and his colleagues show. The inhalation or injection of nicotine as a stimulus to release of vasopressin by the supraoptico-hypophyseal system, as quantitated by Lewis and Chalmers,[17] is best interpreted if compared with the response to a known dose of exogenous vasopression. Thomas [18] stresses the comparison of the response to a placebo with the response to Pitressin. Remission or relapse following a prolonged course of treatment with Pitressin in oil has been employed as a diagnostic sign; but Barlow and de Wardener [14] point out that this procedure is disturbing to many patients and holds the danger of overhydration in some. The latter workers found that the relatively simple test of measuring serum osmolality was as good a way as any to separate the patients with diabetes insipidus (higher than normal) from those with primary polydipsia (lower than normal). Inevitably, good clinical judgment is essential for arriving at a sound diagnosis. Clinical characteristics are important: the compulsive water drinker is much more prone to be psychoneurotic and usually develops his symptoms slowly; the patient with diabetes insipidus usually has an abrupt onset and is said to insist on ice water.[18] The third patient (E. A.) of Díes et al. gave responses to acute testing that indicated a partial lesion of the neurohypophysis and she had x-ray evidence of a lesion in that site; these together supported a diagnosis of diabetes insipidus. Yet remission following a course of Pitressin in oil and a subsequent relapse under emotional stress led to the final diagnosis of primary psychogenic polydipsia.

In the polyuric and polydipsic patient a definitive differential diagnosis is essential to correct treatment. And only correct treatment will restore physiologic (and social) freedom to the patient by permitting the elaboration of a hypertonic urine—even as in the bird and in other terrestrial mammals.

J. R. E.

THE NEW EDITOR, ASSISTANT EDITOR, AND EDITORIAL BOARD

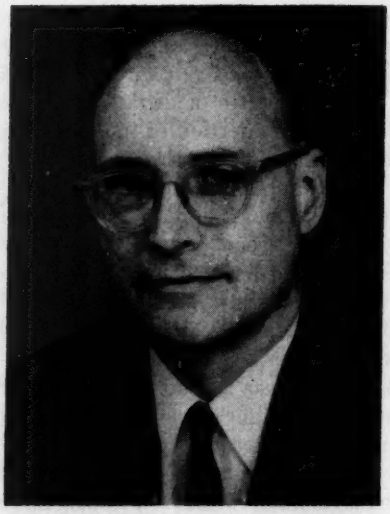
THE ANNALS OF INTERNAL MEDICINE, The American College of Physicians, and Maurice Pincoffs seemed inseparable. When, after 27 years as Editor of the ANNALS, Dr. Pincoffs announced his anticipated retirement at the end of August, 1960, the Board of Regents faced a most difficult task

[15] Brown, W. E., Rynearson, E. H.: A procedure for the diagnosis of diabetes insipidus. Proc. Mayo Clin. **19**: 67–68, Feb. 9, 1944.

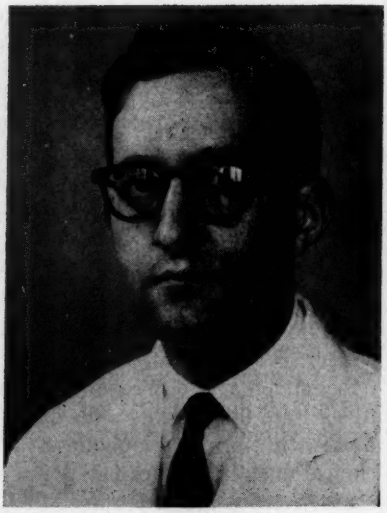
[16] Hickey, R. C., Hare, K.: The renal excretion of chloride and water in diabetes insipidus. J. Clin. Invest. **23**: 768–775, Sept., 1944.

[17] Lewis, A. A. G., Chalmers, T. M.: A nicotine test for the investigation of diabetes insipidus. Clin. Sci. **10**: 137–144, Feb., 1951.

[18] Thomas, W. C., Jr.: Diabetes insipidus. J. Clin. Endocr. **17**: 565–582, 1957.



J. RUSSELL ELKINTON, M.D., F.A.C.P., Editor



EDWARD J. HUTH, M.D., F.A.C.P., Assistant Editor

in choosing his successor. Maurice Pincoffs had been all the things an outstanding editor should be: a man with a scientific and judicial mind, an able clinician, an outstanding teacher, and an expert in telling a story. He brought the ANNALS to its eminence in scientific reporting and in circulation, and with this achievement came great prestige to the College.

Under the able chairmanship of Chester M. Jones, the Committee on Publications, after a meticulous search, recommended to the Board of Regents the appointment of J. Russell Elkinton of Philadelphia as Editor and Edward J. Huth of Philadelphia as Assistant Editor of the ANNALS OF INTERNAL MEDICINE. The Board of Regents in November, 1959, approved these recommendations. In addition the Regents authorized the establishment of an editorial board to assist the Editor, the members to be appointed at a subsequent date.

Selection of an editor whose home is in Philadelphia will permit union of the editorial offices and the College headquarters in Philadelphia with great advantage to each; an additional advantage is proximity to the printers of the ANNALS, the Lancaster Press, in Lancaster, Pennsylvania.

The new Editor is a Philadelphian and a well known leader and expert in the general field of fluid and electrolyte metabolism and renal disease. Since 1952 he has been Associate Professor of Medicine in the University of Pennsylvania School of Medicine where he is also Chief of the Chemical Section of the Department of Medicine. Dr. Elkinton graduated with an A.B. degree from Haverford College in 1932 and from Harvard with an M.D. degree in 1937. After three years at the Pennsylvania Hos-

pital in Philadelphia as an intern and resident, he became in 1940 a National Research Council Fellow in the Medical Sciences at Yale University School of Medicine. For the next eight years as a staff member at Yale he received a rigorous scientific training under John P. Peters and Francis G. Blake in the Department of Internal Medicine, and returned to Pennsylvania in 1948. During the period of 1949 to 1959 he held the position of an Established Investigator of the American Heart Association. From 1954 to 1958 he served as a member of the Study Section on Metabolism and Nutrition of the National Institutes of Health. In 1957 for seven months while on sabbatical leave in England, Russell Elkinton worked at Cambridge University with Professor R. A. McCance in the Department of Experimental Medicine. This experience and many other trips to England and Europe, and the fact that his wife is English, have kept him in close touch with leaders in medicine across the Atlantic.

During a very active career in teaching and research, Dr. Elkinton has been honored by election to the American Society for Clinical Investigation, the Association of American Physicians, the American Physiological Society, the College of Physicians of Philadelphia, and his local, state, and national medical associations. Since 1949 he has been a Fellow of The American College of Physicians. His interests beyond medicine have extended to the Society of Friends, of which he has been an active member, to his hobbies of photography, camping, and fishing, and to his family.

As Editor of the ANNALS, Russell Elkinton has a background of extensive research and clinical study in his chosen field. Review of his papers indicates sound scientific work, good reports, obvious understanding and respect for the work of others, a facility for clear expression, and imagination. He is coauthor with T. S. Danowski of the book, *Body Fluids: Basic Physiology and Practical Therapeutics.* As a member of the editorial boards of *Circulation* (since 1951) and of the *American Journal of Medicine* (since 1956), the new Editor has had personal experience with the problem of selection of material for outstanding medical scientific journals.

Edward Huth, the Assistant Editor, is associated professionally with Russell Elkinton in the Chemical Section of the Department of Medicine at the University of Pennsylvania. A graduate of Wesleyan University in Connecticut and of the University of Pennsylvania School of Medicine, he has spent most of his medical career in that institution; he is now Assistant Professor of Medicine. In 1957–1958 during the tenure of a United States Public Health Service special fellowship Dr. Huth spent a year with Professor Charles Dent of the University College Hospital, London. In 1955 Dr. Huth became an Associate of The American College of Physicians and a Fellow in 1960. He is a member of Phi Beta Kappa and Alpha Omega Alpha. His hobbies are music and photography.

To these two men the Board of Regents, the members of the College, and the profession in internal medicine generally, look with hope and con-

fidence. With the aid of an editorial board now under selection it can be anticipated that the ANNALS OF INTERNAL MEDICINE will clearly and understandingly reflect developments in scientific medicine, in research, in clinical investigation, and in the practice of internal medicine during the next twenty years. Changes in the ANNALS are anticipated because medicine changes. The ANNALS under Dr. Pincoff's editorship assumed a position of leadership. It is the expectation of the Board of Regents that the new Editor and Assistant Editor are well prepared for their tasks and will continue that leadership and develop it to the fullest.

DWIGHT L. WILBUR, F.A.C.P., Chairman
Committee on Publications

BOOK REVIEWS

Medicine as an Art and a Science. By A. E. CLARK-KENNEDY, M.D., F.R.C.P., and C. W. BARTLEY, D.M., M.R.C.P. 425 pages; 14.7 × 22.7 cm. 1960. J. B. Lippincott Company, Philadelphia and Montreal. Price, $6.25.

The medical "textbook seems to have become far too long, factual, and mentally indigestible to be read from cover to cover." This observation has moved these English authors to write a short book which should serve as a remedy.

The textbooks they describe are known to everyone; they are encyclopedias, assemblages of essays on diverse diseases tied to each other only by the kinship of organ or system. Each essay is an abstraction, and the patient as a person is notably obscured by the synthetic accounts of his disorders. Yet the student for whom these texts are written will have to treat, eventually, not diseases, but patients. If not the textbooks, do the medical faculties teach the student how to see the disorder in and of that unique person, the patient? Or do they teach him how to recognize the abstraction, a "disease," as a derangement of chemistry and physiology in a two-legged torso? Increasingly, medical faculties are ill-fitted for the better way of teaching. They now largely comprise bands of technical virtuosi, and the picture of the patient they give to their students is not the whole man in disorder, but the faltering organ in a metabolizing corpus. If the student does not learn from teachers or from his textbooks the *practice* of medicine, the care of *persons* with disease, he must go out and learn it by himself. And the price at which he learns it is apt to be met by the patient, psychically, physically, and fiscally.

The ideal textbook of medicine has not been written. It would set forth a chronologic account of man's life from conception to death in old age. In this framework of growth and decline, it would describe the disorders, whether they arise from internal defects or external hazards, likely to beset man at each phase of his life. This textbook would not suffice alone for the teaching of the practice of medicine. It would be supplemented by a second text, for the fourth year, on the analysis of symptoms and signs, the efficient routes to diagnosis, and the conduct of therapy. The present textbook of pathology, with its abstracted view of disease, would give way to a text more closely resembling textbooks of medicine as they are now known and would include, in addition to the morphologic picture of disease, the derangements of metabolism and function.

In their new text, Clark-Kennedy and Bartley have sketched out a syllabus for the ideal textbook of medicine, and have suggested an approach to the patient and his disease which should more surely help the student to go from the laboratory to the patient's bedside. They begin with "The Patient and His Disease." Their theme, here, is that ". . . organic diseases are not entities which exist apart from patients. They are not things which 'breed' true to type like birds and beasts and flowers. That idea, although it dies hard even in the medical mind, is now completely out of date. Diseases are not that; not even the infectious ones which are so often said to be 'caught.' Rather, organic disease is always a reaction between an individual (with his particular genetic weakness) and some risk or risks, known or unknown to him, to which he has succumbed in his environment, action on and reaction by his body now leading to alteration in him for the worse, as judged on all human standards."

From this view, the authors proceed, in the bulk of the text, to place disease states into the matrix of human life. True to their thesis, they describe man's ills, each briefly, not as little packages of "etiology, pathogenesis, diagnosis, and treatment," but as disorders stemming from man's inner flaws and outer threats.

To complete their work, they advise the student on how to examine the ill person and on how to give proper weight to symptoms and physical findings, so that he may

reach a diagnosis or may suspend judgment, if that be the better end. Treatment is presented not in detailed recipes but in simple and logical principles to be followed. Some pages on the care of "The Very Ill Patient" and "The Dying Man" close the text.

Beside the clear and broad virtues of this book stand some minor flaws in its details. Osteoporosis is far more commonly a cause of pathologic fracture than "over-action of a parathyroid gland" (p. 75). Hydrochloric acid and strong sodium and potassium hydroxide destroy tissue, but not "by rapid oxidation" (p. 82). In aspirin poisoning, sodium bicarbonate is not given intravenously "to stop dangerous hyperventilation of the lungs" (p. 352), but to correct a metabolic acidosis. And the surgeon will be puzzled to read that "the thyroid gland must be explored" to find a parathyroid adenoma (p. 387).

Of less concern but exotic in the American scene are some characteristically English terms and points of view. The American reader may not know that an "aperient" is a laxative or that "acute specific rheumatism" is our acute rheumatic fever. Heroin cannot be used in this country for analgesia. In the United States a child's delay in learning to talk is most unlikely to be due to the influence of "a foreign 'Nanny.'" Despite our reputation abroad as wealthy people, we cannot afford the cost of "Nannies." The authors are sympathetic to the problems of the neurotic patient, even recommending psychoanalysis at times, but as they repeatedly point to "lack of self-discipline" as the cause of many a neurotic disorder, we hear faint British overtones advising that the only real remedy is to go out, stiffen up, and carry on.

These comments cannot smother the qualities of this little book. It is written in a clear and simple style; it says what we as physicians know but what we often fail to teach. The second year student should pick it up with his left hand as he puts down his pathology text with his right, and he should read it again before he accepts his diploma. His father, in practice 20 years, should read it, too, and recall that "diseases" are the problems that confront man as he walks through life.

EDWARD J. HUTH, M.D.

Medical History-Taking. By IAN STEVENSON, M.D. 273 pages; 24 × 16 cm. 1960. Paul B. Hoeber, Inc., Medical Division of Harper & Bro., New York. Price, $6.50.

In this attractively produced and eminently readable little volume, Ian Stevenson, Professor of Psychiatry at the University of Virginia, has applied himself to an important and largely untouched area of clinical medicine. Until the publication of this book there had been no work combining the organic-diagnostic requirements of medical history-taking with the insights into interviewing technics gained by modern psychiatry. Dr. Stevenson has synthesized the two with conspicuous success. His book should be of value not only to the medical student for whom it seems primarily designed, but for any physician who would like to improve his practice of the "art of medicine."

The book begins with an excellent short chapter on the nature of the doctor-patient relationship and moves on to a description of the processes involved in taking the history of the present illness, as well as the family and personal history. Various topics of great practical usefulness are discussed with unusual clarity and perceptiveness. These include: (1) a consideration of the patient's concept of his illness and how this affects his description of it; (2) a section on methods of guiding the interview and how to deal with overly talkative or excessively taciturn patients; (3) a description of methods for enlisting the cooperation of the patient in a consideration of emotional difficulties in his life; and (4) consideration of the virtues of reassurance, via history-taking, the vices of premature reassurance, and how to tell the (often not

obvious) difference. The high point of the book is reached in Dr. Stevenson's description of history-taking in his own major area of research, the psychophysiological (psychosomatic) disorders. These 17 pages constitute probably the finest discussion of this topic in the literature.

The major failing of the book is a discrepancy between the often encyclopedic quantities of information which the author asserts "should" be obtained, and the inadequacy of the conceptual scheme whereby this information is to be ordered. Certain information is clearly of greater value for certain purposes than is other information, and this hierarchy of values is crucial to the sequence of inquiry. The experienced clinician will no doubt use the suggested inquiries (correctly) as a reference source from which to choose according to the needs of the situation. The medical student, on the other hand, may well be overwhelmed by the amount of detail he is exhorted to obtain, and he may succeed only at the price of that very empathy which the author seeks to encourage. These considerations do not materially detract from the overall excellence of the book. It should have a long and useful life.

ALBERT J. STUNKARD, M.D.

Surgical Diseases of the Pancreas. By JOHN M. HOWARD, M.D., F.A.C.S., GEORGE L. JORDAN, M.D., F.A.C.S., and nine other contributors. 607 pages; 18.5 × 26 cm. 1960. J. B. Lippincott Company, Philadelphia. Price, $20.00.

This book was written for clinicians and clinical investigators who desire a background in the surgical treatment of pancreatic disease. More than two-thirds of the book are devoted to acute and chronic pancreatitis and pancreatic carcinoma. Islet-cell tumors are listed in an 82-page tabulation that was collected from the literature as recently as 1958. The authors, each from a different institution, have made original contributions to the subject on which they write. Except for the chapters on pancreatic physiology and pancreatic resection, little reference is made to studies in animals. Congenital anomalies, meconium ileus, pancreatic trauma, and the Zollinger-Ellison syndrome are discussed in individual chapters.

The internist will find the discussion of the differential diagnosis of acute pancreatitis useful, particularly in integrating the results of the serum amylase test with the clinical findings. The clinical manifestations of pancreatic carcinoma are well documented both with personal observations and those collected from the literature. Both authors have drawn heavily on clinical material in charity and Veterans Administration hospitals, which fact should be considered in applying their conclusions to situations in private practice.

The standard work in this subject has been the monograph by Cattell and Warren on *Surgery of the Pancreas,* based largely upon their experiences at the Lahey Clinic. The present book is more comprehensive in its discussion of etiology and diagnosis and devotes more space to collections of data from the world literature. The authors' recommendations for the surgical treatment of pancreatitis without gallstones are based on the failure of other methods rather than on the success of their own approach.

The quality of the paper is excellent and the illustrations including drawings, photographs, and reproductions of roentgenograms are of high quality. Graphs and tables are widely used and clearly labeled and arranged. The index is adequate.

This book will be useful to the physician who must diagnose and treat pancreatic disease, particularly in its acute stages, and it represents a consensus of current surgical practice. Since many patients with acute pancreatic disease are seen primarily by surgeons, it is a valuable reference for the internist and the gastroenterologist. However, for the diagnosis of chronic pancreatic disease, it will not replace standard references in gastroenterology.

FRANK P. BROOKS, M.D.

Congenital Malformations. (Ciba Foundation Symposium). By G. E. W. Wolstenholme, O.B.E., and Cecilia M. O'Connor, B.Sc. 292 pages. 1960. Little, Brown and Company, Boston. Price, $9.00.

Birth is so abrupt an event in man that a special group of disorders, the congenital malformations, has been defined in relation to it. In many ways the term is unfortunate in that it designates a specialty without a specialist, and many cases live and die inadequately studied in the no-man's land between obstetrics, pediatrics, pathology, and, in Scotland, the Registrar General. To overcome this neglect the Ciba Foundation brought together diverse specialists for a symposium; their papers are now presented, along with the associated discussions.

Authoritative articles may be found on such diverse, yet relevant, studies as the human chromosomes, the runt in the mouse, and the mechanisms of both the genesis and the prevention of malformation in the rat. The subject is particularly difficult, and any critic who cannot see any obvious connection between some of the data presented and congenital malformations in man should appreciate that it was because so little was known that the symposium was called.

Experimentally the problem is made difficult by the limitations of conventional experimental animals; those which are viviparous are usually polytocous with very short gestation periods, and when malformations appear they rarely have any close analogy in man; and, while there are as many ways of embarrassing an embryo as of killing a cat, the relevance of these laboratory experiments to the natural hazards of the womb is far from obvious. If anything is found, the experience of public apathy and commercial contempt which has followed the work of Doll and Bradford Hill demonstrating that lung cancer is mainly an optional disease is hardly encouraging to those workers who feel that diets rich in insecticides, antibiotics, synthetic estrogens, preservatives, coloring agents, and detergents are perhaps not optimal.

Some readers may be surprised at the absence of radiation as a subject matter in view of the public concern over experimental war, and the very much higher dosage imposed for diagnostic reasons. This apparent omission does, however, merely exemplify the increasing opinion that the commonest congenital abnormalities are unlikely to be influenced by such insults. The absence of any paper on systemic contraceptives and hormone exposure devised either to diagnose pregnancy or prevent abortion is a more serious omission but again the critic has difficulty in finding contributions which could readily be rejected to make room for such a large subject.

This review can be summarized in a single sentence: the publication conforms to the standards we have learned to expect of the Ciba Foundation and, as such, deserves recognition and dissemination.

J. H. Edwards, M.D.

Clinical Applications of Bronchology. By Dezso Kassay, M.D. 225 pages; 24 × 16 cm. 1960. The Blakiston Division, McGraw-Hill Book Company, Inc., New York. Price, $15.00.

In the first 80 pages of this handsome little volume Doctor Kassay presents the anatomy, physiology, roentgenology, and technical aspects of endoscopy. The remaining 128 pages are devoted to clinical problems, under the following headings: Diseases with Valvular Respiratory Mechanisms, Infectious and Allergic Bronchitis, Pneumonia, Pulmonary Abscess, Bronchiectasis, Pulmonary Tuberculosis and Mycosis, Bronchial Tumors, Foreign Bodies, and Differential Diagnosis. All of the chapters are well illustrated with diagrams and roentgenograms, as well as gross and microscopic pathologic specimens. An outstanding feature is the high quality of the bronchograms used in many of the illustrations.

This is a mature, concise, and well written book by an author who has practiced

his specialty in both Europe and the United States. It presents a broad clinical viewpoint. Because of its brevity certain details are eliminated which would be desirable from the standpoint of the endoscopist; yet its point of view is sound and conveys quite adequately information about bronchology which would interest internists, pediatricians, radiologists, anesthesiologists, and surgeons.

The concluding portion of the book consists of 102 selected references and a careful index.

JOSEPH P. ATKINS, M.D.

Physical Signs in Clinical Surgery. 13th Ed. By HAMILTON BAILEY, M.D., F.R.C.S., F.A.C.S.–F.R.S.E. 928 pages; 22 × 15 cm. 1960. The Williams & Wilkins Co., Baltimore, Md. Price, $14.50.

The appearance since 1927 of 13 editions and 11 reprintings, together with five foreign editions, should testify overwhelmingly to the popularity of this volume.

Although originally written for students beginning their clinical years, it is an excellent text for house officers and graduates as well. It would seem desirable that every medical student have ample time really to study and to refer again and again to this book. It is superbly illustrated with 1,142 illustrations, and certainly a great deal of study and effort was spent in so nicely correlating the pictures with the text. The subject material is arranged in an organized, regional manner to include pertinent data of all systems necessary to a well performed physical examination. Nearly 300 pages are devoted to lesions of the skeletal, vascular, and nervous systems, all of them well illustrated.

HARRY C. HULL, M.D.

A Syllabus of Laboratory Examinations in Clinical Diagnosis: Critical Evaluation of Laboratory Procedures in the Study of the Patient. Rev. Ed. Edited by LOT B. PAGE, M.D., and PERRY J. CULVER, M.D. 580 pages; 28 × 18.5 cm. 1960. Harvard University Press, Cambridge, Mass. Price, $12.50.

This is a revised edition of the *Syllabus of Laboratory Examinations in Clinical Diagnosis* previously edited by Thomas Hale Ham. It has been rewritten and enlarged by 33 contributors. The first edition was designed as a text for medical students taking a course in laboratory diagnosis. The present book is aimed at a wider audience, with the addition of new chapters on the laboratory evaluation of inflammation and necrosis and the interpretation of cardiac catheterization and pulmonary function tests.

The mechanisms and meaning of laboratory tests and procedures in relation to the pathologic physiology of disease are well covered. When possible, the clinical interpretations of the tests are summarized in tables. Technics which can be performed simply with a minimum of laboratory equipment are discussed in detail, while only the principles of the more complicated procedures are given. Extensive lists of references at the ends of the chapters include important recent reviews. Sixteen physicians from the faculty of the Harvard Medical School are listed as the critics who reviewed sections of the book.

The chapters have been carefully edited to avoid repetition, and the cross-indexing is complete. The printing and the format are excellent.

This volume will be valuable to anyone, regardless of the level of his training, who must evaluate the results of laboratory examinations. It is perhaps unfortunate that what was once an excellent, though modestly priced, laboratory manual has now been enlarged into an expensive textbook.

HOWARD RAWNSLEY, M.D.

Dietary Proteins in Health and Disease. By JAMES B. ALLISON, Ph.D., and WILLIAM H. FITZPATRICK, Ph.D. 71 pages; 23.5 × 15.5 cm. 1960. Charles C Thomas, Springfield, Ill. Price, $4.50.

This little monograph, written by an expert on proteins in nutrition, is simply written and is a delightful review of the subject.

Except for a short chapter on protein reserves and a short chapter on nitrogen balance the authors avoid the more controversial topic of protein malnutrition. For example, little is said about essential amino acid requirements in terms of limits. The authors, however, supply a complete bibliography which includes 290 references to all the more important aspects of dietary proteins.

The book is well written and should be of value to anyone working in the fields of nitrogen and amino acid utilization in health and disease. It will also be of value to those interested in the controversy on the definition of optimal nutrition.

LEWIS BARNESS, M.D.

Leukemia Cutis. By SAMUEL M. BLUEFARB, M.D., F.A.C.P. 482 pages; 22.4 × 14.5 cm. 1960. Charles C Thomas, Springfield, Ill. Price, $18.50.

Leukemia Cutis by Dr. Samuel M. Bluefarb is a scholarly and encyclopedic treatise covering all aspects of the skin manifestations of the lymphoma group. In separate chapters the history, pathogenesis, and specific cutaneous lesions associated with each of the major types of leukemia are described. In addition, an extensive section deals with the many and varied nonspecific cutaneous manifestations of this group of diseases.

The book is a detailed review of broad scope which should be exceedingly useful to dermatologists, internists, and oncologists. Dr. Bluefarb is eminently qualified for the task to which he has set himself. He has extensive personal experience in this area and is the author of many excellent investigative studies. His prose style is lucid, the book is excellently organized, and the 760 references quoted cover the entire gamut of the literature appropriate to the problem.

The physical make-up of the book is attractive and the printing is clear and easy to read. It is unfortunate that many of the half-tone illustrations, at least in my copy, were only of medium quality.

In summary, *Leukemia Cutis* can be highly recommended as a scholarly and complete review of a very difficult subject.

FREDERICK URBACH, M.D.

Tumors of the Odontogenic Apparatus and Jaws. By JOSEPH L. BERNIER, D.D.S. 107 pages, with 136 illustrations. 26 × 20 cm. 1959. Armed Forces Institute of Pathology, Washington 25, D. C. Price, $1.00.

In this fascicle the odontogenic and nonodontogenic tumors of the oral regions are discussed. The material is subdivided into two sections: tumors of the hard oral tissues and tumors of the soft oral tissues. The first section includes the cysts and the odontogenic and nonodontogenic tumors of the jaws; the second section is concerned with lesions of the lips, tongue, oral mucosa, and gingiva. The author uses the term "tumor" in its broadest sense and therefore non-neoplastic lesions such as cysts and granulomas have been included.

More than half of this 107-page fascicle is concerned with cysts and odontogenic tumors of the jaws. These are classified on the basis of the embryologic development of the jaws and teeth. In the majority of cases each disease entity is discussed from the standpoint of natural history, histogenesis, and microscopic appearance. Clinical diagnosis, prognosis, and treatment are not discussed. The presentation is brief and concise, and is generously illustrated by excellent photomicrographs. Wherever possible, roentgenograms and clinical photographs are also included. The author has considered the simple and aneurysmal bone cysts under the heading of "Ecto-

dermal Nonodontogenic Cysts," and the torus, osteoma, fibrous dysplasia of the jaws, Paget's disease of bone, giant cell tumor, and eosinophilic granuloma under the heading of "Ectodermal Nonodontogenic Tumors." It is most unlikely that these lesions are ectodermal in origin.

The brief and concise manner in which the material is presented and the excellent illustrations render this fascicle very useful to the general and the oral pathologist. This fascicle is also recommended to the roentgenologist and the general practitioner of medicine and dentistry.

GEORGE A. KRIKOS, D.D.S., Ph.D.

BOOK NOTICES

Drugs in Current Use 1961. Edited by WALTER MODELL, M.D., F.A.C.P. 154 pages; 14 × 21 cm. 1960. Springer Publishing Company, Inc., New York. Price, $2.25.

This manual is a listing of drugs, official and nonofficial, now employed. Brief notations give the nature, actions and uses, dangers, routes of administration, preparations, and dosage of each drug. Entries of proprietary names refer the reader to entries under generic names.

For what use was this manual written? Too big for the pocket or bag, too sketchy for reference, it will not serve the physician well as a handbook of drug therapy. Nevertheless, the pithy, blunt, and honest comments on the redundant drugs coming from the drug house steeplechase contrast refreshingly with the formal and inhibited essays in most books of this type.

E. J. H.

The Johnson Recording Oscillometer: Its Use in the Study of Arterial Circulation. By CARL A. JOHNSON, M.S., M.D. 112 pages; 23.5 × 16 cm. 1959. Permagon Press, Inc., New York. Price, $5.00.

This treatise describes the construction and uses of a plethysmograph with optical recordings for use in the digits and the more proximal parts of the limbs.

The arterial pulsations found in various arterial diseases and in other clinical conditions are described. The instrument has also been adapted to record pulsatile changes in the orbit, over the temporal artery, and over the forehead, although the application of the technic to carotid arterial obstruction is not mentioned.

H. EDWARD HOLLING, M.D.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. So far as is practicable those of special interest are reviewed, but it is not possible to discuss them all.

Aids to Medicine. 7th Ed. By J. H. BRUCE, M.D., M.R.C.P. 391 pages; 16.5 × 10.5 cm. 1960. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, $3.50.

Biology of Pyelonephritis. EDWARD L. QUINN, M.D., F.A.C.P., and EDWARD H. KASS, M.D., Ph.D., M.A. (Hon.), F.A.C.P., editors for the Henry Ford Hospital International Symposium. 708 pages; 24 × 16 cm. 1960. Little, Brown and Company, Boston. Price, $18.00.

The Central Nervous System and Behavior. Transactions of the Third Conference Sponsored by the Josiah Macy, Jr. Foundation, with the Cooperation of the National Science Foundation. Edited by MARY A. B. BRAZIER, D.Sc., Neurophysiological Laboratory, Massachusetts General Hospital, Boston, Mass. 475

pages; 23.5 × 16 cm. 1960. Josiah Macy, Jr. Foundation, New York. Price, $7.50.

The Choice of a Medical Career. Essays on the Fields of Medicine. Edited by JOSEPH GARLAND, M.D., Sc.D. (Hon.), and JOSEPH STOKES, III, M.D. 231 pages; 21 × 14 cm. 1961. J. B. Lippincott Company, Philadelphia. Price, $5.00.

Clinical Disorders of the Pulmonary Circulation. Edited by RAYMOND DALEY, M.A., M.D. (Camb.), F.R.C.P., JOHN F. GOODWIN, M.D. (Lond.), F.R.C.P., and ROBERT E. STEINER, M.D.N.U.I., M.R.C.P., D.M.R., F.F.R. 364 pages; 25.5 × 19.5 cm. Little, Brown and Company, Boston. Price, $14.00.

Clinical Toxicology. By C. J. POLSON, M.D. (Birm.), F.R.C.P., M.R.C.S., and R. N. TATTERSALL, O.B.E., M.D. (Lond.), F.R.C.P. 589 pages; 23 × 15 cm. 1961. J. B. Lippincott Company, Philadelphia. Price, $10.00.

Congenital Malformations of the Heart. Vol. II. Specific Malformations. By HELEN B. TAUSSIG, M.D. 1,049 pages; 27 × 18 cm. 1960. Published for The Commonwealth Fund by the Harvard University Press, Cambridge, Mass. Price, $17.50.

Dermatology. Diagnosis and Treatment. 2nd Ed. By MARION B. SULZBERGER, M.D., F.A.C.P., JACK WOLF, M.D., VICTOR H. WITTEN, M.D., and ALFRED W. KOPF, M.D. 615 pages; 23 × 15.5 cm. 1961. The Year Book Publishers, Inc., Chicago, Ill.

Epidemiologic Methods. By BRIAN MACMAHON, M.D., Ph.D., D.P.H., THOMAS F. PUGH, M.D., M.P.H., and JOHANNES IPSEN, D.M., Dr. Med., M.P.H. 302 pages; 24.5 × 16 cm. 1960. Little, Brown and Company, Boston. Price, $7.50.

Endocrine Dysfunction and Infertility: Report of the Thirty-fifth Ross Conference on Pediatric Research, held under joint auspices of the Department of Obstetrics and Gynecology and the Department of Pediatrics, Ohio State University College of Medicine, Columbus, Ohio, January 28–29, 1960. Director: RICHARD H. SPITZ, M.D.; Editor: SAMUEL J. FOMON, M.D.; Associate Editor: JAMES E. JEFFRIES, M.D. 86 pages; 23 × 15.5 cm. Ross Laboratories, Columbus, Ohio.

Haemopoiesis: Cell Production and Its Regulation. Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.R.C.P., and MAEVE O'CONNOR, B.A. 490 pages; 21 × 14 cm. 1960. Little, Brown and Company, Boston. Price, $11.00.

Handbuch der Inneren Medizin, Vol. 9. Edited by G. v. BERGMANN, M. D., W. FREY, M.D. and H. SCHWIEGK, M.D. 12 pages; 29.5 × 21 cm. 1960. Springer-Verlag, Heidelberg, West Berlin.

Hospital Infection: Causes and Prevention. By R. E. O. WILLIAMS, M.D., M.R.C.P., R. BLOWERS, M.D., L. P. GARROD, M.D., F.R.C.P., and R. A. SHOOTER, M.D. 299 pages; 22 × 14.3 cm. 1960. The Year Book Publishers, Inc., Chicago, Ill. Price, $7.50.

Neurovascular Compression Syndromes of the Shoulder Girdle. By LOUIS M. ROSATI, M.D., and JERE W. LORD, M.D. 168 pages; 23 × 15.5 cm. 1960. Grune & Stratton, New York. Price, $7.25.

Valvular Disease of the Heart in Old Age. By P. D. BEDFORD, M.D., M.R.C.P., and F. I. CAIRD, D. M., M.R.C.P. 194 pages; 21 × 14 cm. 1961. Little, Brown and Company, Boston. Price, $7.50.